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(54) Title: PHARMACEUTICAL COMPOUNDS

(57) Abstract: This invention relates to certain novel imidazoline compounds and analogues thereof, to their use for the treatment of diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present, to pharmaceutical compositions comprising them, and to processes for their preparation.

PHARMACEUTICAL COMPOUNDS

This invention relates to certain novel imidazoline-type compounds and analogues thereof, to their use for the treatment of diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present, to pharmaceutical compositions comprising them, and to processes for their preparation.

It is generally accepted that the control of blood glucose levels for the treatment of patients diagnosed with type II diabetes will have a beneficial effect. Established oral therapies for treating type II diabetes either improve insulin action or cause enhanced insulin secretion. Agents currently approved as therapies for type II diabetes patients that cause an enhanced insulin secretion contain a sulphonlyurea moiety. These compounds act by depolarising the beta cell by modulating closure of the K-ATP channel. Additional compounds that act at the K-ATP channel, which are not sulphonylureas compounds and which have a fast onset of activity and a short duration of action, are under consideration for treatment of type II diabetes. One such compound is (-)-N-(trans-4-isopropylcyclohexanecarbonyl)-D-phenylalanine (A-4166) (Brit. J. Pharm. 1997,120,137-145).

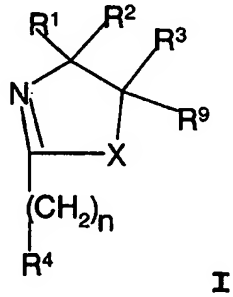
All agents that function at the molecular level by modulating the K-ATP channel have the potential for inducing hypoglycemia. Hypoglycemia is the major cause of adverse reactions in patients receiving sulphonylurea therapy and the prevalence of hypoglycemic episodes can be as high as 20% of patients. Compounds that potentiate insulin secretion under high glucose conditions and have little or no effect at low blood glucose levels would offer a distinct advantage in the treatment of type II diabetes.

Compounds of the present invention potentiate the secretion of insulin from beta cells under high glucose conditions and have minimal effect under low glucose conditions.

The compounds are also operable in additional disease states where impaired glucose disposal is present. For example, these include cardiovascular disease where above normal glucose levels are present or initial insulin resistance has occurred. The compounds can also be used to treat post operative insulin resistance induced by anaesthesia.

The present invention provides compounds of the following Formula (I), and the use of said compounds in the treatment of diabetes, especially Type II diabetes, diabetic complications, and metabolic disorders or related diseases in particular where impaired glucose disposal is present.

The present invention provides compounds of the following Formula (I):



I

wherein

R^1, R^2, R^3, and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together with the carbon atoms to which they are attached, combine to form a C_{3-7} carbocyclic ring and R^2 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together optionally form a bond and R^2 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^2, together with the carbon atom to which they are attached combine to form a C_{3-7} spirocarbocyclic ring and R^3 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

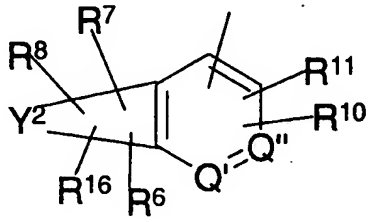
R^3 and R^9, together with the carbon atom to which they are attached, combine to form a C_{3-7} spirocarbocyclic ring and R^1 and R^2 are each independently hydrogen or C_{1-8} alkyl;

X is -O-, -S-, or $-NR^5-$;

R^5 is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl, and an amino protecting group;

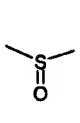
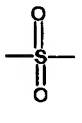
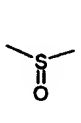
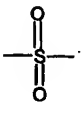
n is 0, 1, or 2;

R^4 is a group of the formula:



Q' and Q" are each independently selected from the group consisting of C, N, and N-O, provided that if one of Q' or Q" is N or N-O, then the other of Q' or Q" must be C, such that Q' and Q" cannot each simultaneously be selected from the group consisting of N and N-O;

Y^2 is $(CH_2)_{n'}$ wherein n' is 3, 4, 5, or 6; such that a 5- to 8- membered ring is formed to provide a bicyclic ring along with the benzene or pyrimidine group to which it is fused, which 5- to 8- membered ring is saturated, partially saturated or unsaturated

and may optionally contain up to two atoms each independently selected from the group consisting of -O-, -S-,  ,  ,  , and -NR^{12}-, wherein each such optional -O-, -S-, atom or  ,  ,  , -NR^{12}- groups replacing any one of the -CH_2- groups comprising Y^2 , provided that the resulting benzofused bicyclic ring is not an indole, and in which any of the -CH_2- groups which comprise Y^2 may be substituted by R^6, R^7, R^8 or R^{16} provided that no more than four H atoms in Y^2 are replaced by said substitution and that the resulting benzofused bicyclic is not naphthalene or quinoline; and any two selected from the group consisting of R^6, R^7, R^8, R^{16} and R^{12} may optionally combine to form a bridge which is comprised of up to four carbon atoms provided that such bridge-forming two of R^6, R^7, R^8, R^{16} and R^{12} are not bound to adjacent atoms, or together with the carbon atom to which they are attached may form a C_{3-7} spirocarbocyclic ring, in which one or two carbon atoms are optionally replaced by oxygen, sulfur, or NR^5, or together with the two adjacent carbon atoms to which they are attached R^6, R^7, R^8, R^{16} and R^{12} may form a C_{1-9} carbocyclic ring, in which one or two of the carbon atoms is optionally replaced by oxygen, sulfur or NR^5, and further provided that at least one of the group consisting of R^6, R^7, R^8, R^{16} and R^{12} is not hydrogen when X is NH, n is 0, and R^1, R^2, R^3, and R^9 are each hydrogen and Q' and Q'' are each C;

R^{12} is selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl, and an amino protecting group;

R^6 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, halo C_{1-8} alkylthio, C_{1-8} alkylsulfinyl, C_{1-8} alkylsulfonyl, C_{3-7} cycloalkoxy, aryl-C_{1-8} alkoxy, halo, halo-C_{1-8} alkyl, halo- C_{1-8} alkoxy, nitro, -$NR^{14}R^{15}$, -$CONR^{14}R^{15}$, aryl C_{1-8} alkyl, optionally substituted heterocyclyl, optionally substituted phenyl, optionally substituted naphthyl, C_{1-8}

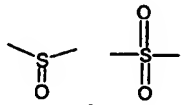
acylamino, haloC_{1-8} acylamino, cyano, hydroxy, COR^{13}, $COOR^{13}$, halo C_{1-8} alkylsulfinyl, halo C_{1-8} alkylsulfonyl, and alkoxyalkyloxy of the formula $CH_3(CH_2)_p$-O-$(CH_2)_q$-O-;

R^7, R^8, and R^{16} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, halo, halo-C_{1-8} alkyl, halo-C_{1-8} alkoxy, optionally substituted phenyl, optionally substituted naphthyl, and optionally substituted heteroaryl;

R^{10} is selected from the group consisting of hydrogen, halo, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cycloalkyl-C_{1-8} alkoxy, halo-C_{1-8} alkyl, halo-C_{1-8} alkoxy, C_{1-8} alkoxy, carbo-C_{1-8} alkoxy, optionally substituted aryl, and optionally substituted heteroaryl;

R^{11} is selected from the group consisting of hydrogen, halo, C_{1-8} alkoxy, C_{3-7}-cycloalkyl, C_{3-7} cycloalkyl-C_{1-8} alkoxy, C_{1-8} alkyl, C_{3-7} cycloalkoxy, hydroxy, halo C_{1-8} alkoxy, carbo-C_{1-8} alkoxy, optionally substituted phenyl, optionally substituted phenyl-C_{1-8} alkyl, optionally substituted phenyloxy, optionally substituted phenyl-C_{1-8} alkoxy, (tetrahydropyran-2-yl)methoxy, C_{1-8} alkyl-$S(O)_m$, optionally substituted aryl-C_{1-8} alkyl-$S(O)_{m'}$, $CH_3(CH_2)_{p'}$-Z^1-$(CH_2)_{q'}$-Z^2-, and Z^3-$(CH_2)_{q''}$-Z^2-;

where

Z^1 and Z^2 are each independently a bond, -O-, -S-,  , sulphoximino, or $NR^{14'}$,

Z^3 is hydroxy, protected hydroxy, $NR^{14'}R^{15'}$, protected amino, SH, or protected SH;

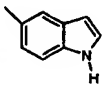
R^{13} is hydrogen, C_{1-8} alkyl, or optionally substituted phenyl;

R^{14} , $R^{14'}$ R^{15} and $R^{15'}$ are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl C_{1-8} alkyl, optionally substituted phenyl, or R^{14} and R^{15} or $R^{14'}$ and $R^{15'}$, respectively, together with the nitrogen atom to which they are attached may combine to form a heterocyclic ring comprising the nitrogen and C_{2-6} alkyl, wherein C_{2-6}alkyl is optionally substituted with one or two C_{1-8} alkyl groups or one carbon atom of the heterocyclic ring is optionally replaced by -O- or -S-;

p and p' are each independently selected from the group consisting of 0, 1, 2, 3, and 4;

q, q', and q''' are each independently selected from the group consisting of 1, 2, 3, 4, and 5;

m, m', and m'' are each independently selected from the group consisting of 0, 1 and 2;

provided that when R^1, R^2, R^3, and R^9 are each hydrogen, X is NH, n is 0, then R^4 is not 4-(benzothiazol-2-yl)benzyl or a group of the formula:  ;

and pharmaceutically acceptable salts and esters thereof.

One embodiment of the present application is the use of a compound of the Formula I or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament for treating diabetes or a related disorder.

Another embodiment of the present invention is a method of treating diabetes or a related disorder, which comprises administering to a patient a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In the above formulae, a "C_{1-8} alkyl" group can be any alkyl group, branched or unbranched, containing up to eight carbon atoms, likewise, $C_{1-n'}$ alkyl is a

branched or unbranched alkyl containing up to n' carbon atoms whereing n' is an integer. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. Preferred values of C_{1-8} alkyl are C_{1-6} alkyl, and most preferably methyl and ethyl.

The term "C_{1-8} alkylthio" has the meaning known to the artisan. That is that one of the carbon atoms is replaced with a sulfur atom.

A "C_{3-7} cycloalkyl" group is a cycyloalkyl group such as cyclopropyl, cyclobutyl, cycloheptyl, cyclohexyl or cyclopentyl.

A "C_{3-7} cycoalkyl-C_{1-8} alkyl" group is one such cycloalkyl group attached through a C_{1-8} alkyl group to the cycloalkyl group. It is especially preferred that the alkyl group is C_{1-6} alkyl.

A "C_{1-8} alkoxy" group is one of the above-mentioned C_{1-8} alkyl groups attached through oxygen to the base molecule, and preferred examples are methoxy and ethoxy.

A "benzofused bicyclic" is a group wherein the ring formed by Y^2 is fused with the aromatic group to which it is attached.

As used herein, "bicyclic" refers to a two ring fused ring system which may be aromatic, partially saturated or saturated.

A "C_{3-7} cycloalkoxy" group is a C_{3-7} cycloalkyl group as mentioned above linked through an oxygen atom to the cycloalkyl as, for example, cyclopropyloxy, cyclopentyloxy and cyclohexyloxy.

A "C_{3-7} cycloalkylC_{1-8} alkoxy" group is a C_{3-7} cycoalkyl-C_{1-8} alkyl as mentioned above linked through an oxygen atom to the base molecule as, for example, cyclohexylmethoxy.

A "carboxy" group is C alkyl

A "carbo(C_{1-8})alkoxy" group is a  group, for example a carbomethoxy or carboethoxy group.

An "optionally substituted aryl" group is a mononuclear or polynuclear aromatic hydrocarbon group, for example phenyl or naphthyl, which is optionally

substituted with from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted phenyl" group is a phenyl which is optionally substituted with from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted naphthyl" group is a naphthyl which is optionally substituted with from one to three substituents independently selected from, the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted COaryl" group is an optionally substituted aryl which is bound to the base molecule through a group of the formula:  . The optionally substituted aryl group is defined herein above.

A "optionally substituted aryl-C_{1-8} alkyl-$S(O)_{m''}$ " group is an optionally substituted aryl which is bound to the base molecule through an alkyl-$S(O)_{m''}$ group, wherein the S- bonds to the base molecule. The optionally substituted aryl group is as defined herein above.

"Heteroaryl" means a four to a ten membered aromatic mononuclear or binuclear ring system in which from one to three atoms of the ring system are each independently selected from the group consisting of nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include, but are not limited to, indolyl, imidazo [1,2-a] pyridinyl, imidazo [1,2-a] pyrimidinyl, imidazolyl, piperazinyl, furanyl, thionyl, isoquinolinyl, benzofuranyl, benzothiophenyl, pyridyl, quinolinyl, oxazolyl, pyrrolyl, isoxazolyl, pyrimidyl, thiazolyl, and benzimidazolyl.

An "optionally substituted heteroaryl" group is a heteroaryl group which is optionally substituted with from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

"Optionally substituted heterocyclyl" means a four to 10 membered mononuclear or binuclear saturated or partially unsaturated ring system in which from one to three atoms of the ring system are each independently selected from the group consisting of nitrogen, oxygen, and sulfur, and which ring system is optionally substituted with from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino. Examples of heterocyclyl groups include, but are not limited to, piperidinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, morpholinyl, homopiperidinyl, tetrahydroquinolinyl, dioxanyl, and tetrahydropyranyl.

An "aryl-C_{1-8} alkyl" group can be, for example, optionally substituted phenyl-C_{1-8} alkyl or optionally substituted naphthyl-C_{1-8} alkyl, such optionally substituted phenyl or naphthyl groups being optionally substituted with one or more, preferably

one to three, substituents selected from, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino. A preferred aryl-C_{1-8} alkyl group is optionally substituted phenyl-$(CH_2)_x$- where x is 1 or 2, most preferably optionally substituted benzyl. Thus, the alkyl group serves as the link between the phenyl or naphtyl and the base molecule.

An "optionally substituted phenyloxy" is a group wherein the phenyl group is attached to the base molecule through an oxygen, and such phenyl group is optionally substituted with one or more, preferably one to three, substituents selected from, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino.

An "optionally substituted phenylC_{1-8} alkoxy" is a group wherein the phenyl group is attached to the base molecule through an alkoxy group, and such phenyl group is optionally substituted with one or more, preferably one to three, substituents selected from, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino.

Of course, it will be understood that "optionally substituted" means that there may be zero non-hydrogen substituents.

An "aryl-C_{1-8} alkoxy" group can be, for example, optionally substituted phenyl-C_{1-8} alkoxy or optionally substituted naphthyl-C_{1-8} alkoxy, such optionally substituted groups being optionally substituted with one or more, preferably one to three, substituents selected from, for example, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino. A preferred aryl-C_{1-8} alkyl group is optionally substituted phenyl-$(CH_2)_x$- where x^- is 1 or 2. Thus, the aryl is linked to the base molecule through the alkoxy group.

A halo group is preferably chloro, bromo, iodo, or fluoro. Halo may more preferably be chloro, bromo, or fluoro.

A halo C_{1-8} alkyl or halo C_{1-8} alkoxy group or halo C_{1-8} alkylthio is a substituent in which one or more, preferably one to three, hydrogen atoms on the C_{1-8}

alkyl moiety is replaced by a halo atom, preferably chloro, bromo or fluoro. Trifluoromethyl is one preferred haloalkyl group.

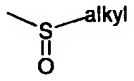
An "alkoxyalkoxy" group is of the formula $CH_3(CH_2)_p$-O-$(CH_2)_q$-O-, where p is 0-4 and q is 1-5, preferred examples being those in which p is 0 or 1 and q is 1-3, especially methoxyethoxy, ethoxyethoxy, ethoxypropoxy, or methoxypropoxy.

A "C_{1-8} acylamino" substituent is preferably of the formula RCONH- where RCO is any appropriate acid residue, RCO containing from 1-8 carbon atoms. Examples of R include C_{1-8} alkyl, in particular methyl or ethyl, acetyl being the most preferred acyl group. R can also be aryl C_{1-8} alkyl, especially benzyl, or R can be halo- C_{1-8} alkyl, especially trifluoromethyl.

A "haloC_{1-8} acylamino" substituent is an acylamino group substituted with from one to three halo. It is preferable that acylamino is substituted with one halo.

The term "carbocyclic" means a carbon ring, which optionally contains unsaturation, if such unsaturation is possible for a given carbocyclic group as described. It is most preferred that carbocyclic refers to a saturated ring system.

The term "spirocarbocyclic" means a ring which is fused to the base molecule through one shared tetravalent carbon atom to form two rings which are annylated by a single carbon atom.

The term "C_{1-8} alkylsulfinyl" has the meaning known to the artisan. That is a group of the formula 

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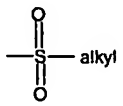
The term "halo C_{1-8} alkylsulfinyl" means that one of the alkyl groups is substituted with a halo. It is most preferred that the halo group is F or Cl.

The term "C_{1-8} alkylsulfonyl" has the meaning known to the artisan. That is a group of the formula 

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The term "halo C_{1-8} alkylsulfonyl" means that one of the alkyl groups is substituted with a halo. It is preferred that the haloalkylsuflonyl group is CF_3SO_2-,

The term "sulfoximino" has the meaning known to the artisan. That is, a group of the formula:  .

The "acyl" moiety, alone or in combination, is derived from an alkanoic acid containing from one to eight carbon atoms. The term "acyl" also includes moieties derived from an aryl carboxylic acid.

As used herein, the term "aryl coupling" shall mean any appropriate method for coupling two aromatic or heteroaromatic rings known to the artisan. Such methods may include, but are not limited to Uhlman, Stille coupling or Suzuki coupling methods. The Suzuki coupling is an especially preferred coupling method. The Suzuki method using Ar-$B(OH)_2$ and Pd catalyst is particularly preferred for use in the synthesis methods described herein. The artisan will appreciate that there are a variety of available Pd catalysts which are acceptable for the Suzuki coupling. One such Pd catalyst which is preferred for the methods described herein is $Pd(PPh_3)_4$.

The term "base molecule" means the ring system to which the named substituent is bound.

The term "indole" has the meaning known to the artisan, that is 2,3-benzopyrrole.

The term "treating", as used herein, describes the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of present invention to prevent the onset of the symptoms or complications, to alleviate the symptoms or complications, or to eliminate the disease, condition, or disorder.

As used herein the term "amino protecting group" means any of the conventional amino protecting groups, see, for instance, T. W. Greene, Protective Groups in Organic Synthesis, chapter 7, John Wiley and Sons, New York, 1981, and by J. W. Barton, Protective Groups in Organic Chemistry, chapter 2, J. F. W. McOmie, ed., Plenum Press, New York, 1973. Examples of such groups include but are not intended to be limited to benzyl and substituted benzyl such as 3,4-dimethoxybenzyl, o-nitrobenzyl, and triphenylmethyl; those of the formula -COOR where R includes such groups as methyl, ethyl, propyl, isopropyl,

2,2,2-trichloroethyl, 1-methyl-1-phenylethyl, isobutyl, t-butyl, t-amyl, vinyl, allyl, phenyl, benzyl, p-nitrobenzyl, o-nitrobenzyl, and 2,4-dichlorobenzyl; acyl groups and substituted acyl such as formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, benzoyl, and p-methoxybenzoyl; and other groups such as methanesulfonyl, p-toluenesulfonyl, p-bromobenzenesulfonyl, p-nitrophenylethyl, p-toluenesulfonylaminocarbonyl, and the like. Preferred nitrogen protecting groups are benzyl, acyl, like benzyloxycarbonyl or t-butyloxycarbonyl, or silyl or acetyl phenyloxycarbonyl.

The term "protected amino" means that the amino group is substituted with an amino protecting group, as defined herein.

As used herein the term "protected hydroxy" means that the hydroxyl group is substituted with any of the conventional hydroxyl protecting groups, see, for instance, T. W. Greene, Protective Groups in Organic Synthesis, chapter 2, John Wiley and Sons, New York, 1981, and by J. W. Barton, Protective Groups in Organic Chemistry, J. F. W. McOmie, ed., Plenum Press, New York, 1973. Examples of such groups include but are not intended to be limited to acetals, ethers such as silyl ethers and the like; esters such as formate, benzoylformate, acetate, phenoxyacetate and the like; carbonates such as methyl carbonate, ethyl carbonate, isobutylcarbonate, benzyl, nitrobenzyl, and the like; and others such as nitrate, borate, phenylcarbamate, tetrahydropyrinyl (THP), trityloxypyrinyl and the like. The artisan will recognise that the art includes other acceptable protecting groups as provided by the cited references.

As used herein the term "protected SH" means that the thiol group is substituted with any of the conventional thiol protecting groups, see, for instance, T. W. Greene, Protective Groups in Organic Synthesis, chapter 6, John Wiley and Sons, New York, 1981, and by J. W. Barton, Protective Groups in Organic Chemistry, J. F. W. McOmie, ed., Plenum Press, New York, 1973. Examples of such groups include but are not intended to be limited to thioethers like benzylthioether, 4-methylbenzylthioether, p-nitrobenzylthioether, diphenylmethylthioether, substituted methyl derivatives such as methoxymethyl (MOM), isobutoxymethyl, 2-tetrahydropyranyl, thioesters like, acetyl, benzoyl, thiocarbonates like t-butoxycarbonyl, and the like.

The compounds of the present invention can be useful for modulating insulin secretion and as research tools. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of preferred compounds and process conditions. The following list of embodiments of this invention is not intended to limit the scope of this invention in any way. Some prefered characteristics of compounds of Formula I are:

(i) R^1 and R^2 are hydrogen and R^3 and R^9 are each hydrogen or methyl;

(ii) R^1, R^2, R^3 and R^9 are each hydrogen;

(iii) X is NH;

(iv) n is 0;

(v) R^6 is selected from the group consisting of halo, nitro, cyano, C_{2-6} alkyl, halo C_{1-6} alkyl, halo C_{1-6} alkoxy, or halo C_{1-6} alkylthio;

(vi) n is 1;

(vii) Y^2 is $(CH_2)_{n'}$ wherein n' is 4, 5, or 6;

(viii) Y^2 is $(CH_2)_{n'}$ wherein n' is 4, 5, or 6 and none of the CH_2 groups are replaced by another atom;

(ix) Q^1 and Q^2 are each C;

(x) Q^1 is N and Q^2 is C;

(xi) Q^1 is C and Q^2 is N;

(xii) R^{10} is selected from the group consisting of C_{2-6} alkyl, halo C_{1-6} alkyl, optionally substituted benzyl, optionally substituted phenyl, and optionally substituted thienyl;

(xiii) R^{10} is selected from the group consisting of hydrogen, methyl, trifluoromethyl, benzyl, 3-chlorobenzyl, phenyl, 4-methylphenyl, 2,4-dichlorophenyl, 3-methyl-2-thienyl, 2,5-dimethyl-3-thienyl, 4-methoxyphenyl, 2-methoxyphenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 3-thienyl, 2-bromophenyl, 4-chloro-3-methylphenyl, 2,4-dimethylphenyl, 2-(trifluoromethyl)phenyl, and 3-fluorophenyl;

(xiv) R^9 is methyl;

(xv) X is O or S;

(xvi) R^6 is CH_3;

(xvii) R^6 is CF_3;

(xviii) R^6 is Cl or Br;

(xix) R^{11} is $H_3C(CH)_{p'}$-O-$(CH)_{q'}$-O- where p' and q' are as defined by Formula I and II above;

(xx) R^{11} is H_3COCH_2-CH_2-O-;

(xxi) R^1 and R^3 together form a bond;

(xxii) R^1 and R^3 together form a C_4-C_7 carbocyclic ring;

(xxiii) R^1 and R^2 together form a C_4-C_7 spirocarbocyclic ring;

(xxiv) Y^2 is $(CH_2)_{n'}$ wherein n' is 4, 5, or 6 and one of the CH_2 groups is replaced by -S-,  or  ;

(xxv) Y^2 is $(CH_2)_{n'}$ wherein n' is 4, 5, or 6 and one of the CH_2 groups is replaced by -O-;

(xxvi) Y^2 is $(CH_2)_{n'}$ wherein n' is 4, 5, or 6 and one of the CH_2 groups is replaced by $-NR^{12}$;

(xxvii) Y^2 is $(CH_2)_{n'}$ wherein n' is 4, 5, or 6 and one of the CH_2 groups is replaced by  ;

(xxviii) Y^2 is $(CH_2)_{n'}$ wherein n' is 4, 5, or 6 and R^7 and R^8 are each C_{1-2} alkyl substituted on non-adjacent carbon atoms of Y^2 and R^7 and R^8 combine to form a C_{2-4} alkyl bridge on Y^2;

(xxix) R^4 is a coumarin group;

(xxx) R^4 is a quinolone group;

(xxxi) Y^2 is $(CH_2)_n$ such that Y^2 forms a C_{5-8} cycloalkyl group which thereby forms a benzofused bicyclic R^4;

(xxxii) the ring that is formed by Y^2 contains one double bond;

(xxxiii) the ring that is formed by Y^2 is unsaturated;

(xxxiv) the ring that is formed by Y^2 is saturated;

(xxxv) the ring that is formed by Y^2 contains two double bonds;

(xxxvi) R^{11} is C_{1-8} alkoxy or halo C_{1-8} alkoxy;

(xxxvii) Q' is N and Q'' is C which is substituted with an R^{10} group;

(xxxviii) Q' is N and Q'' is C is substituted with an R^{10} group wherein R^{10} is selected from the group consisting of optionally substituted phenyl wherein phenyl is substituted with a group selected from C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo and trifluoromethyl;

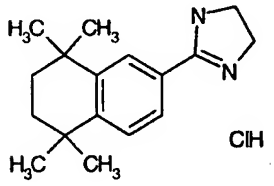
(xxxix) the ring that is formed by Y^2 is $(CH_2)_n$ such that Y^2 forms a C_{5-8} cycloalkyl group wherein R^7 and R^8 each replace a hydrogen on the same CH_2 group of Y^2, thereby forming a substituted bicyclic R^4;

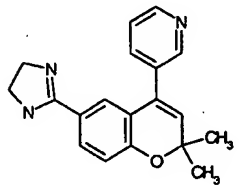
(xl) Z^2 is selected from the group consisting of a bond and -O-;

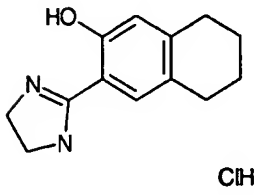
(xli) R^5, $R^{5'}$, or R^{12} is not an amino protecting group;

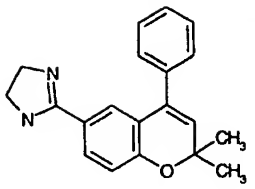
(xlii) Preferred compounds of the present invention include any one of the following compounds:

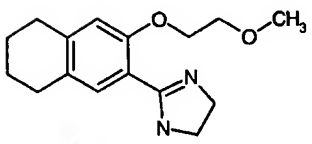
MolStructure



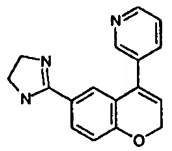








CIH



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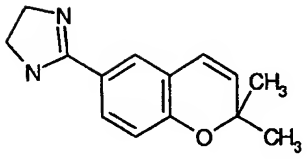

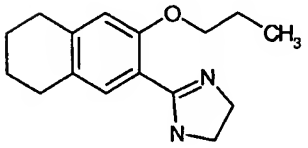

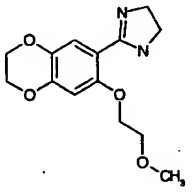

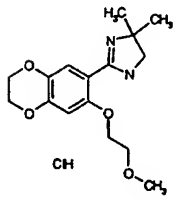

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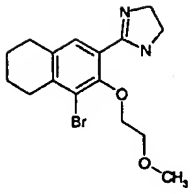

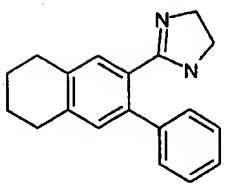

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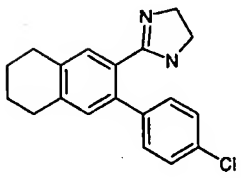

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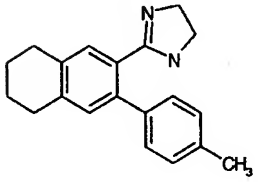

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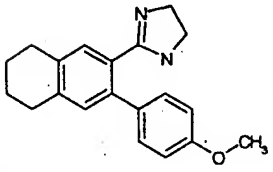

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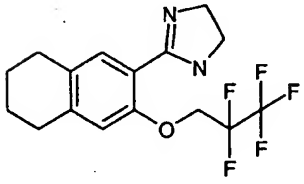

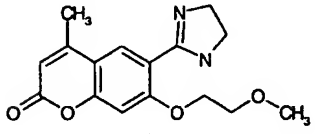

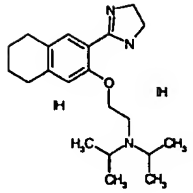

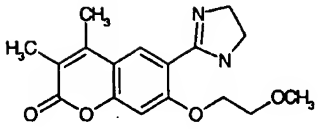

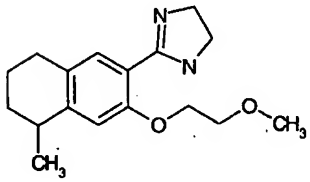

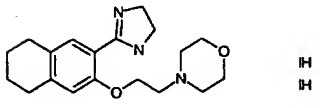

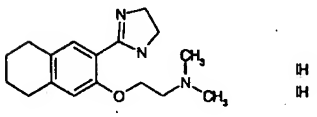

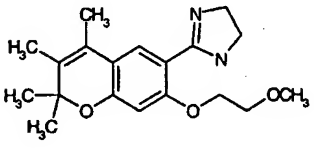

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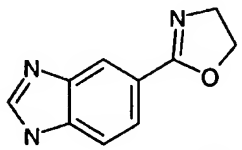

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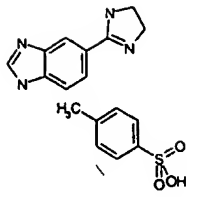

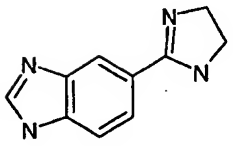

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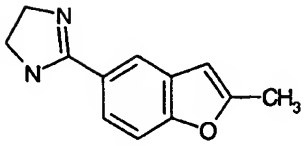
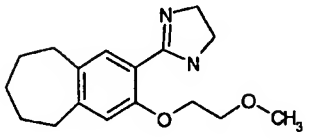
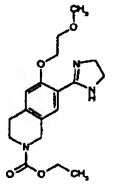
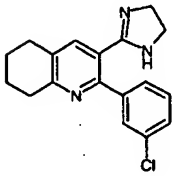
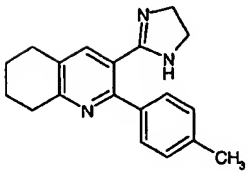
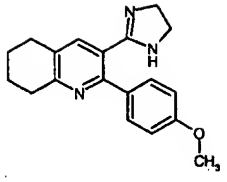






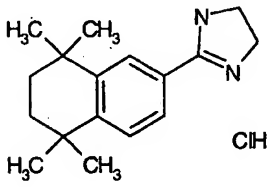






(i) especially preferred compounds of the present invention include any one of the following:

MolStructure



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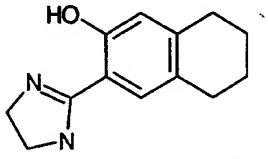

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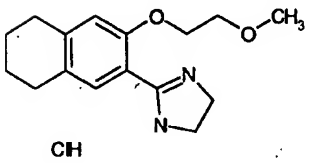

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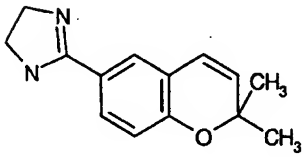
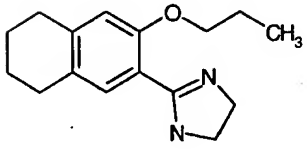
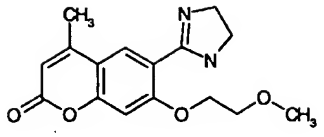
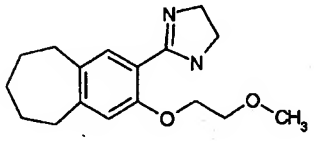
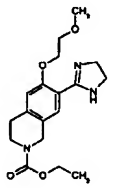
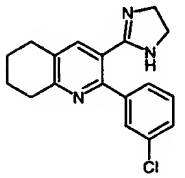


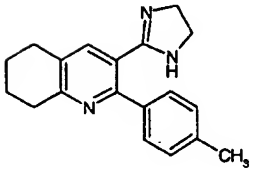


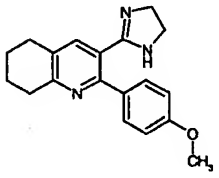












By virtue of their acidic moieties, some of the compounds of Formula I include the pharmaceutically acceptable base addition salts thereof. Such salts include those derived from inorganic bases such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines such as aliphatic and aromatic amines, aliphatic diamines,

hydroxy alkamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylenediamine, cyclohexylamine, ethanolamine and the like.

Because of a basic moiety, some of the compounds of Formula I can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para- bromophenylsulfonic, carbonic, succinic, citric, benzoic, acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-l-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

In addition, it is recognised that compounds of the present invention may form a variety of solvates with a number of different solvents. Representative solvates can be useful as final embodiments of the present invention or as intermediates in the isolation or preparation of the final embodiments of this invention. For example solvates can be prepared with lower alcohols such as ethanol and with alkyl esters such ethylacetate.

It is recognised that various stereoisomeric forms of the compounds of Formula I may exist. The compounds may be prepared as racemates and can be conveniently used as such. Therefore, the racemates, individual enantiomers (including, but in no way limited to atropisomers), diastereomers, or mixtures thereof form part of the present invention. Unless otherwise specified, whenever a compound

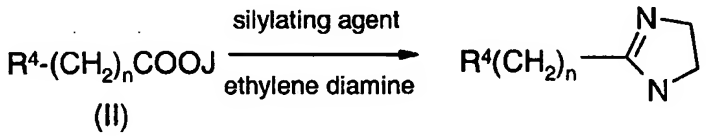
is described or referenced in this specification all the racemates, individual enantiomers, diastereomers, or mixtures thereof are included in said reference or description.

In addition to the pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification.

General methods of synthesis for the compounds of the present invention are described by Schemes I through VI, below.

Compounds of Formula I wherein X is NH; wherein X is as defined above and the other Formula I substituents have the definitions given above, can be prepared according to scheme I.

Scheme I



wherein R^4 and n are as defined herein for Formula I, and J is C_{1-8}alkyl, aryl, or aryl C_{1-8}alkyl.

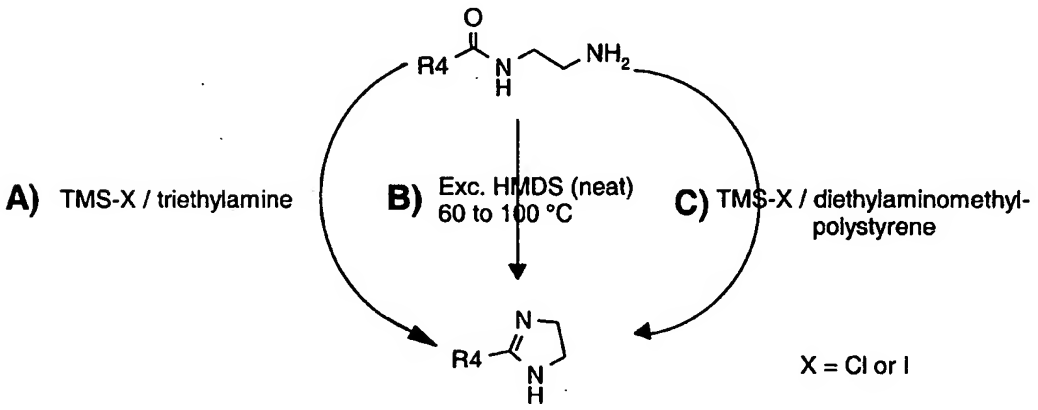
The transformation is further described by Scheme Ia.

Cyclisation is induced by a silylating agent or a mixture of silylating agents, optionally in the presence of an soluble or insoluble base, e.g. triethyl amine or dimethylaminomethyl polystyrene and a solvent. Useful reagents are e.g. described in FLUKA Chemika, "Silylating Agents" (1995) ISBN 3-905617-08-0 and the literature cited therein.

In a more prefered embodiment, these silylating agents are trimethyl silyl halogenides, TMS-X (e.g. trimethyl silyl chloride or trimethyl silyl iodide) or hexamethyl disilazane, HMDS or trimethyl silyl diethylamine, TMS-DEA or mixtures of them. In the most prefered embodiment the reactions are carried out either in

methylene chloride with excess TMS-Cl or, more prefered, TMS-I in presence of triethyl amine or dimethylaminomethyl polystyrene at ambient temperature, or in neat HMDS or HMDS/TMS-Cl 100/1, without additional base and solvent at 50°C to reflux, preferably at 70°C to 90°C. In some cases, using TMS-X as cyclizing reagent, excessive reagent has to be added in several portions within a period of time (up to about a week) to ensure complete conversion. The process described herein is compatible to many functionalities present in an organic molecule, e.g. unprotected hydroxy, unprotected amino, olefinic double bond, cyano, nitro, aromatic halogen, amide and is sucessful in some cases, when conventional methods failed (Chem. Pharm. Bull. **1980, *28***, 1394-1402).

Scheme Ia



It is important to note that in Scheme Ia, the variable X does not have the same meaning as set forth in Formula I, rather X is as defined in the Scheme Ia.

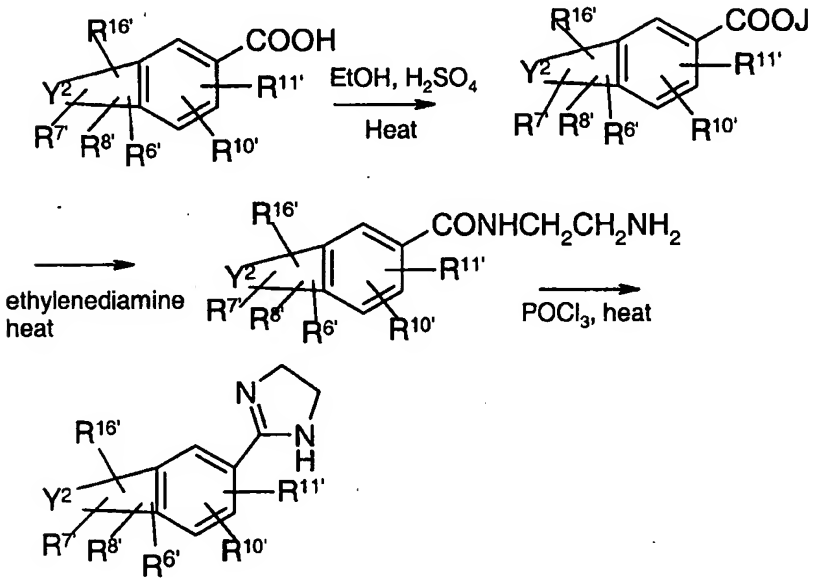
The process described in Scheme Ia affords numerous advantages over similar methods known in the art. The transformation can be achieved in high yield and under mild conditions, whereas, methods known in the art require the use of extreme conditions or reagents

The artisan will recognise that there are other processes which could be used to prepare desired compounds. See for example, J.Med.Chem. **1990, 33**, 2501-8 (uses $(CH_2NH_2)_2$); J.Chem.Soc. **1947**, 497 (uses $(CH_2NH_2)_2$ and TsOH/200-220^{0}C); J.Am.Chem.Soc. **1953, 75**, 2986-8 (uses $(CH_2NH_2)_2$ and 200-220^{0}C); J.Med.Chem. **1987, 30**, 1482-9 (uses $Al(CH_3)_3$ and $(CH_2NH_2)_2$); Tetrahedron Lett. **1990, 31**, 1771-

74 (uses $(CH_2NH_2)_2$); J.Org.Chem. **1987**, **52**, 1017-21 ($La(OSO_2CF_3)_3$ and $(CH_2NH_2)_2$); Zh.Prikl.Khim. **1970**, **43**, 1641 (CA:**73**:77138r) (uses $(CH_2NH_2)_2$ and strongly acidic cation exchange reagent); Arch.Pharm. **1986**, **319**, 830-34 (uses $(CH_2NH_2)_2$); J.Heterocycl.Chem. **1990**, **27**, 803-5 (uses $(CH_2NH_2)_2$); Tetrahedron **1995**, **51**, 6315-36 (uses two step process with 1) H_2S and H_3CI then 2)$(CH_2NH_2)_2$).

The skilled artisan will also appreciate that a hydroxy substituted group can be used to prepare desired compounds claimed by this invention. Such process is illustrated by Scheme II below.

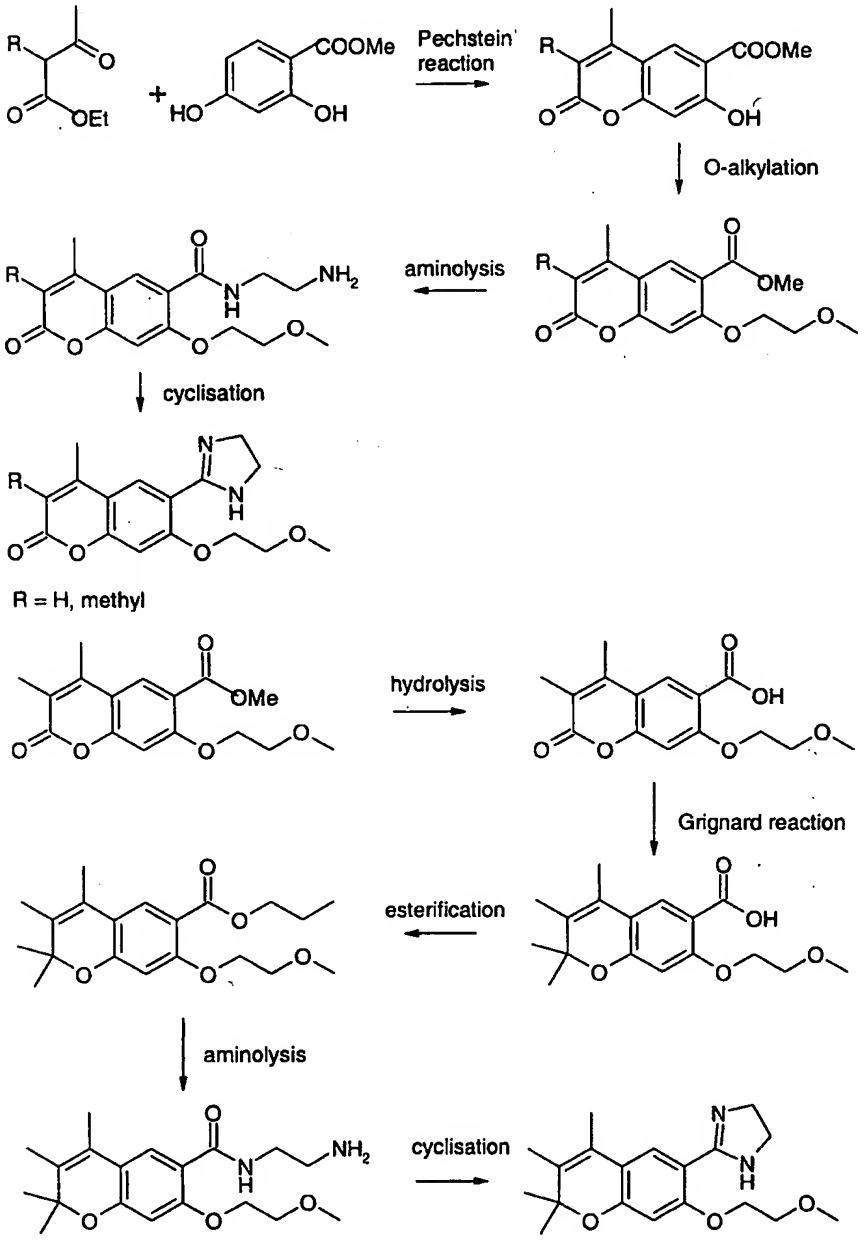
Scheme II



wherein $R^{6'}$, $R^{7'}$, $R^{8'}$, $R^{10'}$, $R^{11'}$, and $R^{16'}$ are R^6, R^7, R^8, R^{10}, R^{11}, and R^{16}, respectively, protected derivatives thereof, or precursor moieties thereto.

Compounds of Formula I having a coumarin group can be prepared using the method generally described by Scheme III. The artisan will appreciate that other derivatives of the coumarin compounds can be prepared using methods known to the artisan.

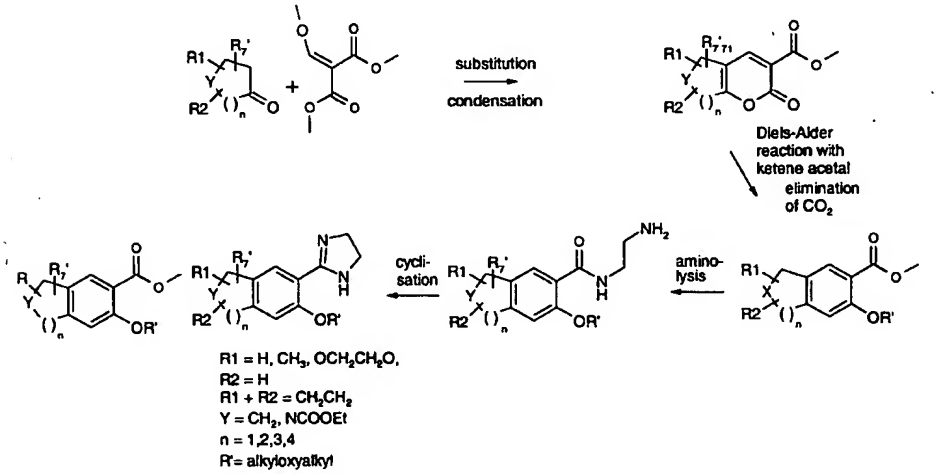
Scheme III



As used in Scheme III, the definition of R is H or methyl. This definition is provided for purposes of illustrating the process of Scheme III.

Benzofused compounds of this invention can be prepared using the Diels Alder reaction as illustrated by Scheme IV. The condensation, aminolysis, and cyclisation methods illustrated by Scheme IV are standard methods known to the skilled artisan. The artisan will appreciate that other intermediates can be used to prepare further Formula I compounds using the illustrated process and methods known to the artisan.

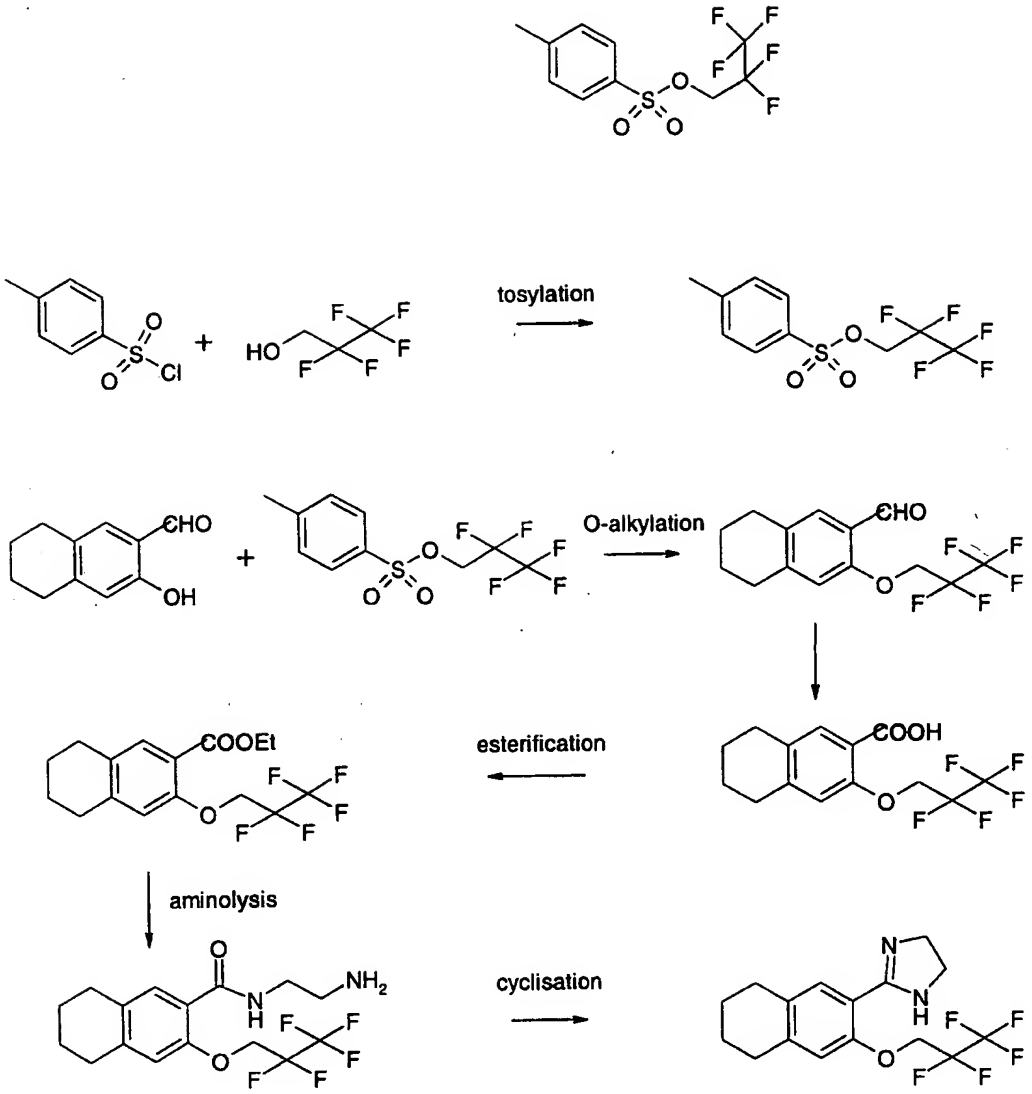
Scheme IV



As used in Scheme IV, R1, R2, Y, n and R' solely have the meanings set forth in Scheme IV. The definitions set forth by Scheme IV are independent of the definitions for R1, R2, Y and n, provided by Formula **I**. R_7' has the meaning of R^7 as shown by Formula **I** herein.

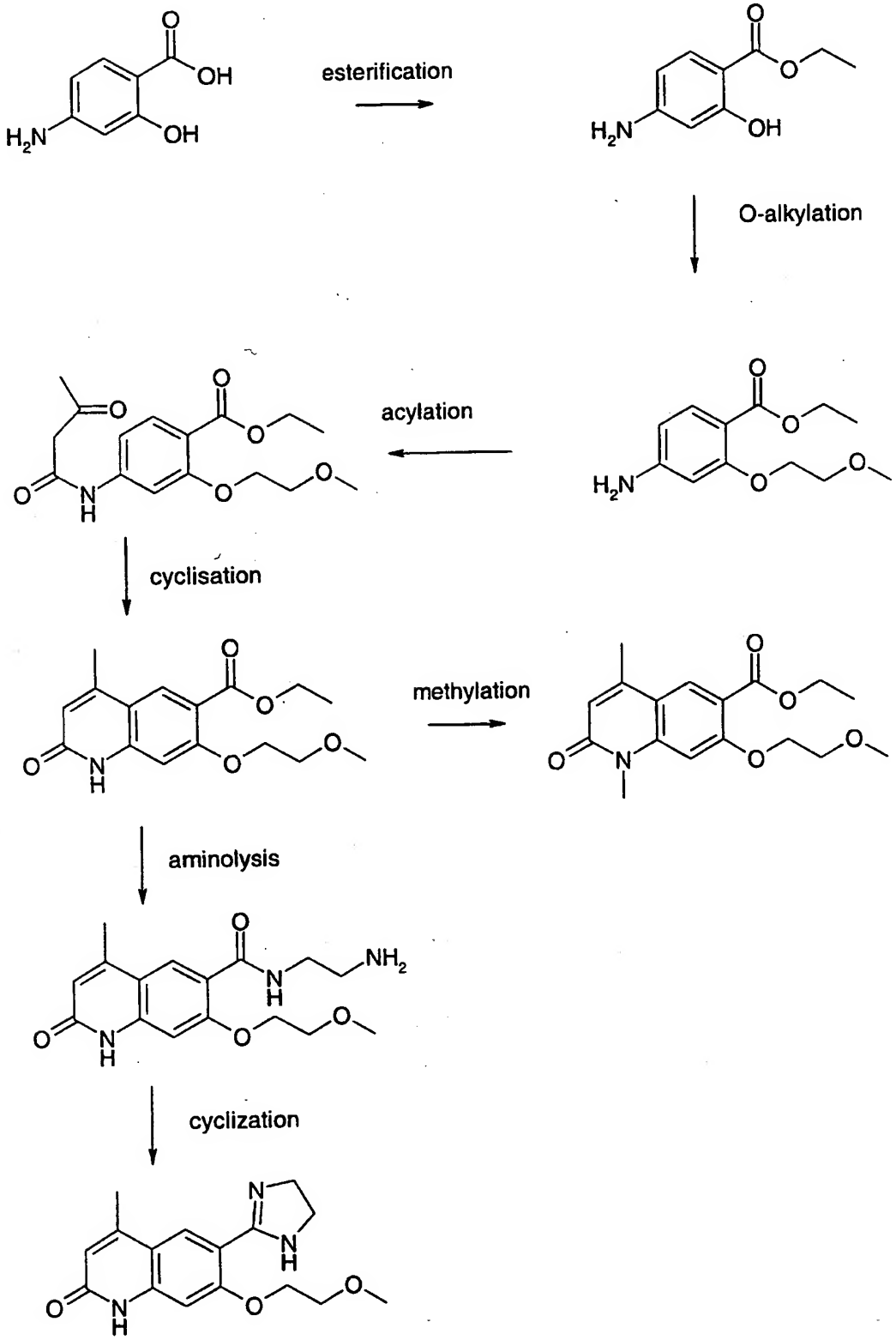
Compounds of Formula **I** having a fluorinated side chain can be prepared using the process as illustrated by Scheme V. The alkylation, acylation, and esterification methods illustrated by Scheme V are standard methods known to the skilled artisan.

Scheme V



Quinolone compounds of Formula I can be prepared using the general method as illustrated by Scheme VI. The cyclisation, acylation, esterification, and alkylation are each standard methods known to the skilled artisan.

Scheme VI


esterification
O-alkylation
acylation
cyclisation
methylation
aminolysis
cyclization

The artisan appreciates that, in some instances, desired isomeric forms may be obtained using separation methods which are generally known.

Additionally, the artisan will recognize that tautomeric forms of the compounds claimed herein are possible, for example, when R^5 is hydrogen. Such tautomeric forms are contemplated and within the scope of the compounds claimed herein.

Compounds of Formula (I) have primary action during hyperglycemia in that they improve glucose tolerance without producing marked reduction in basal plasma glucose levels.

Compounds of the invention were active in screens for activity using assays based on the use of BTC6 cells, for example as described by Poitout,V et al. Diabetes 44:306-313 (1995) and D'Ambra ,R et al Endocrinology, 126: 2815-2822 (1990)] and rat Langerhans islets, for example as described by Lacy, P.E and Kostianovsky,M. Diabetes (1967),and as described in more detail in hereinbelow, and in an Intravenous Glucose Tolerance Test as described hereinbelow.

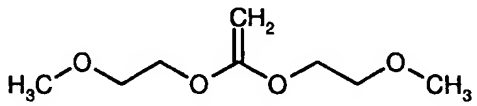
The invention further includes a method of treating diabetes in which an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof is administered to a patient requiring such treatment.

Preparations and Examples

The following examples and preparations are provided merely to further illustrate the invention. The scope of the invention is not construed as merely consisting of the following examples. In the following examples and preparations, melting point, nuclear magnetic resonance spectra, mass spectra, high pressure liquid chromatography over silica gel, gas chromatography, N,N-dimethylformamide, palladium on charcoal, tetrahydrofuran, ethyl acetate, thin layer chromatography and elemental analysis are abbreviated M.Pt. or m.p., NMR, MS, HPLC, GC, DMF, Pd/C, THF, EtOAc, TLC and EA respectively. The terms "EA", "TLC", "NMR", and "MS",

when being utilised in the preparations, indicate that the data indicated was consistent with the desired structure. Reported melting points are uncorrected and yields are not optimised.

Preparation 1: **1,1-Bis-(2-methoxyethoxy)ethene**



A solution of 100 g (0.51 mol) 2-bromoacetaldehyde diethylacetal in 200 g (2.62 mol) 2-methoxyethanol was filled into a distillation apparatus followed by addition of 550 mg (2.76 mmol) toluene-4-sulfonic acid. The reaction mixture was heated to 150°C, and within 4 h 41.6 g (0.91 mol) ethanol were distilled off during the progress of the reaction. Remaining ethanol and the excess of 2-methoxyethanol were removed *in vacuo* (14 mbar, 70°C), and the resulting 2-bromoacetaldehyde bis-(2-methoxyethyl)acetal was dissolved in 200 ml dry toluene and vigorously stirred with 585 mg (5.5 mmol) sodium bicarbonate. The suspension was filtered and the filtrate treated with 3.2 g (9.92 mmol) tetrabutylammonium bromide followed by addition of 68.4 g (610 mmol) potassium tert.-butoxide in six portions within 30 minutes at room temperature. The slurry was heated to 110°C for 3 h, cooled to room temperature, and filtered. The sovent was removed under reduced pressure, and the remaining red oil was distilled *in vacuo*. The distillation afforded the title acetal as a colorless oil that solidified in the refrigerator.

Yield: 37.4 g (51 %); b.p. 75 °C (9 mbar)

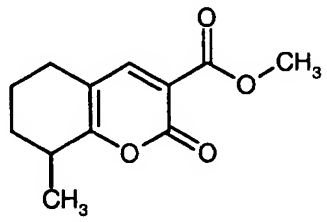
Preparation 2: **General procedure for the condensation of cyclic ketones with 2-methoxymethylene dimethylmalonate**

To a solution of freshly prepared lithium diisopropylamide (1.2 equivalents) in tetrahydrofuran (2 ml / mmol) was added at – 50 °C the cyclic ketone (1.0 equivalent) in tetrahydrofuran (1 ml / mmol). It was warmed to – 30 °C within 1.5 h, treated with 2-methoxymethylene dimethylmalonate (1.2 equivalents), and warmed to room temperature within 10 h. The mixture was poured into 5 % aqueous HCl and extracted with tert.-butylmethyl ether. After removal of the solvent, the product was either recrystallized from tert.-butylmethyl ether or purified by chromatography.

The following intermediates were prepared by this procedure:

Preparation 2a

Methyl 8-Methyl-2-oxo-5,6,7,8-tetrahydro-2H-benzo[b]pyran-3-carboxylate

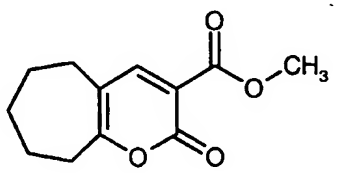


from 3.00 g (26.5 mmol) 2-methylcyclohexanone and purified by recrystallisation from tert.-butylmethylether.

Yield: 3.30 g (56 %); MS 222 (M^+)

Preparation 2b

Methyl 2-Oxo-2,5,6,7,8,9-hexahydro-cyclohepta[b]pyran-3-carboxylate

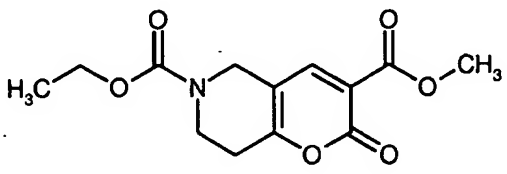


from 1.10 g (4.95 mmol) cycloheptanone and purification via chromatography (silica gel, ethyl acetate / hexane 1:2)

Yield: 0.85 g (62 %); MS 222 (M^+)

Preparation 2c

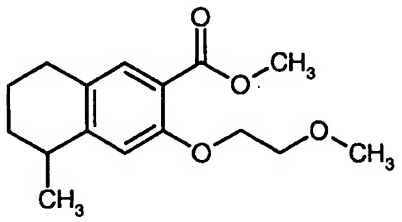
Methyl 6-Ethoxycarbonyl-2-oxo-7,8-dihydro-2H,5H-pyrano[3,2-c]pyridine-3-carboxylate



The primary condensation product obtained from 1.27 g (7.42 mmol) 1-ethoxycarbonyl-4-piperidone was dissolved in 35 ml toluene and heated for 4 h in the presence of 0.3 equivalents toluene-4-sulfonic acid. After removal of the solvent the remaining brown oil was chromatographed (silica gel, ethyl acetate / hexane 1:1) to afford the title compound.

Yield: 711 mg (47 %); MS 281 (M^+)

Preparation 3: Methyl-3-(2-Methoxyethoxy)-5-methyl-5,6,7,8-tetrahydronaphthyl-2-carboxylate



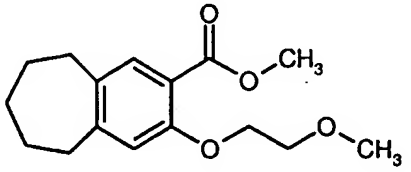
A solution of 1.20 g (5.4 mmol) methyl 8-methyl-2-oxo-5,6,7,8-tetrahydro-2H-benzo[b]pyran-3-carboxylate and 2.33 g (16.0 mmol) 1,1-bis-(2-methoxyethoxy)ethene in 30 ml dry xylene was heated for 14 h. The solvent was removed under reduced pressure and the title compound obtained by chromatography (silica gel, ethyl acetate / hexane 1:3).

Yield: 842 mg (47 %); MS 278 (M^+)

The following intermediates were prepared in the same manner:

Preparation 3a

Methyl 3-(2-Methoxyethoxy)-6,7,8,9-tetrahydro-5H-benzocycloheptene-2-carboxylate

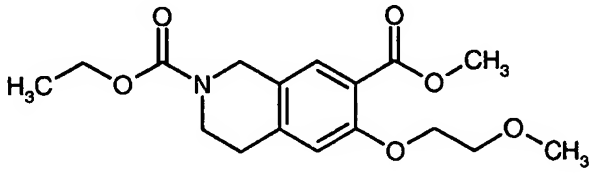


from 1.20 g (5.40 mmol) methyl 2-oxo-2,5,6,7,8,9-hexahydro-cyclohepta[b]pyran-3-carboxylate;

Yield: 1.11 g (62 %); MS 278 (M^+)

Preparation 3b

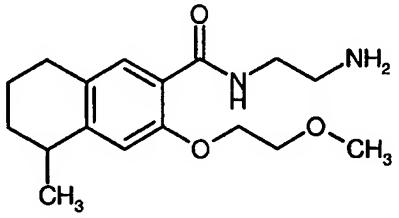
Methyl 2-Ethoxycarbonyl-6-(2-methoxyethoxy)-3,4-dihydro-1H-isoquinoline-7-carboxylate



from 1.05 g (3.73 mmol) methyl 6-ethoxycarbonyl-2-oxo-7,8-dihydro-2H,5H-pyrano[3,2-c]pyridine-3-carboxylate and 1.61 g (11.1 mmol) 1,1-bis-(2-methoxyethoxy)ethene and chromatographic purification with ethyl acetate / hexane 1:1;

Yield: 591 mg (47 %); MS 337 (M^+)

Preparation 4: 2-Aminoethyl 3-(2-Methoxyethoxy)-5-methyl-5,6,7,8-tetrahydronaphthyl-2-carboxamide



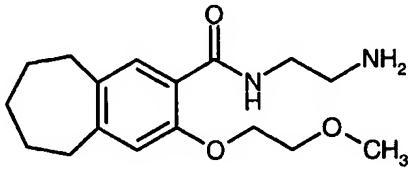
A solution of 120 mg (0.43 mmol) methyl 3-(2-methoxyethoxy)-5-methyl-5,6,7,8-tetrahydronaphthyl-2-carboxylate in 1 ml 1,2-diaminoethane was stirred at 85 °C for 16 h under an argon atmosphere. After removal of the solvent *in vacuo* the title compound was obtained by chromatography (silica gel, dichloromethane / 10% ethanolic ammonia 95:5).

Yield: 90 mg (69 %); MS 306 (M^+)

The following intermediates were prepared in the same manner:

Preparation 4a

2-Aminoethyl 3-(2-Methoxyethoxy)-6,7,8,9-tetrahydro-5H-benzocycloheptene-2-carboxamide

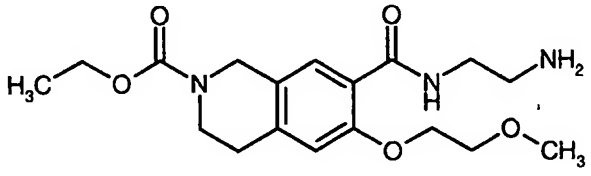


from 200 mg (0.72 mmol) methyl 3-(2-methoxyethoxy)-6,7,8,9-tetrahydro-5H-benzocycloheptene-2-carboxylate;

Yield: 160 mg (73 %); MS 306 (M^+)

Preparation 4b

2-Aminoethyl 2-Ethoxycarbonyl-6-(2-methoxyethoxy)-3,4-dihydro-1H-isoquinoline-7-carboxamide

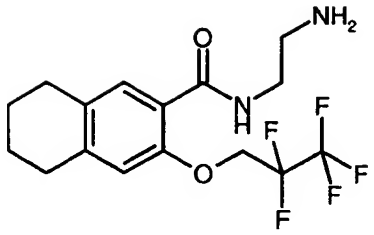


from 135 mg (0.4 mmol) methyl 2-ethoxycarbonyl-6-(2-methoxyethoxy)-3,4-dihydro-1H-isoquinoline-7-carboxylate at room temperature;

Yield: 40 mg (27 %); MS 366 (M^++1)

Preparation 4c

2-Aminoethyl 3-(2,2,3,3,3-Pentafluoropropoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxamide

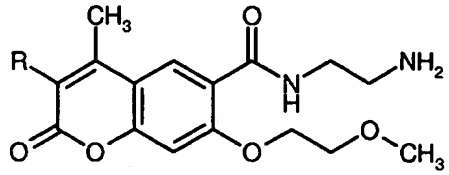


from 250 mg (7.10 mmol) ethyl 3-(2,2,3,3,3-pentafluoropropoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate;

yield: 0.11 g (42 %); MS 366 (M^+)

Preparation 4d

2-Aminoethyl 7-(2-Methoxyethoxy)-4-methyl-2-oxo-2H-benzo[b]pyran-6-carboxamide (R = H)



from of 8.2 g (28.0 mmol) methyl 7-(2-methoxyethoxy)-4-methyl-2-oxo-2H-benzo[b]pyran-6-carboxylate in 70 ml 1,2-diaminoethane for 2 days at room temperature;

Yield: 7.4 g (82 %); MS 320 (M^+)

Preparation 4e

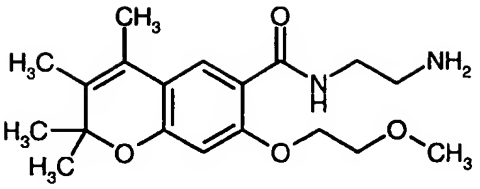
2-Aminoethyl 3,4-Dimethyl-7-(2-methoxyethoxy)-2-oxo-2H-benzo[b]pyran-6-carboxamide (R = CH_3)

from 0.46 g (1.37 mmol) methyl 3,4-dimethyl-7-(2-methoxyethoxy)-2-oxo-2H-benzo[b]pyran-6-carboxylate in 4 ml 1,2-diaminoethane for 3 days at room temperature;

Yield: 0.23 g (50 %); MS 334 (M^+)

Preparation 4f

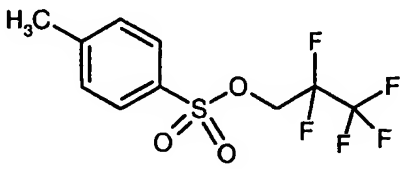
2-Aminoethyl 7-(2-Methoxyethoxy)-2,2,3,4-tetramethyl-2H-benzo[b]pyran-6-carboxamide



from 125 mg (0.36 mmol) propyl 7-(2-methoxyethoxy)-2,2,3,4-tetramethyl-2H-benzo[b]pyran-6-carboxylate;

Yield: 60 mg (48 %); MS 349 (M^++1)

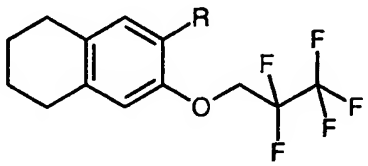
Preparation 5: 2,2,3,3,3-Pentafluoropropyl Toluene-4-sulfonate



A solution of 3.40 g (22.6 mmol) 2,2,3,3,3-pentafluoropropanol, 8.64 g (45.3 mmol) toluene-4-sulfonyl chloride, and 8.96 g (113 mmol) pyridine in 50 ml dry dichloromethane was stirred at 0 °C for 5 h followed by 16 h at room temperature. The reaction mixture was poured into 10 % aqueous potassium carbonate solution, and the organic layer was extracted with 5 % aqueous citric acid and dried over sodium sulfate. The solvent was removed under reduced pressure to leave the crystalline title compound.

Yield: 4.6 g (67 %); MS 304 (M^+)

Preparation 6: 3-(2,2,3,3,3-Pentafluoropropoxy)-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde (R = CHO)



A solution of 0.50 g (2.80 mmol) 3-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde (prepared according to a method from Eur. J. Med. Chem. – Chim. Ther. 18 (1983), 79), 1.28 g (4.20 mmol) 2,2,3,3,3-pentafluoropropyl toluene-4-sulfonate,

and 580 mg (0.20 mmol) potassium carbonate in 20 ml dry DMF was warmed to 80 °C for 60 h followed by 5 h at 120 °C. The reaction mixture was poured into water and extracted with ethyl acetate. The solvent was removed *in vacuo*, and the remaining oil was purified by chromatography (silica gel, hexane / ethyl acetate 9:1) to afford the title compound.

Yield: 0.66 g (77 %); oil; MS 308 (M^+)

Preparation 7: 3-(2,2,3,3,3-Pentafluoropropoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylic Acid (R = COOH)

To a solution of 0.66 g (2.14 mmol) 3-(2,2,3,3,3-pentafluoropropoxy)-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde in 10 ml acetone was added at 0 °C a solution of 0.54 g (5.36 mmol) chromium trioxide in a mixture of 1.6 ml water and 0.45 ml concentrated sulfuric acid. The dark red solution was stirred for 10 min, quenched with 5 ml isopropanol and stirred for another 5 min while the solution turned green. The solvents were removed under reduced pressure and the remaining solid was dissolved in ether and 0.1 N aqueous hydrochloric acid. The organic layer was dried over sodium sulfate and evaporated *in vacuo* to afford the title carboxylic acid.

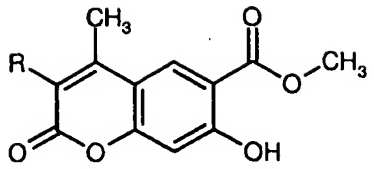
Yield: 0.25 g (36 %); MS 324 (M^+)

Preparation 8: Ethyl 3-(2,2,3,3,3-Pentafluoropropoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (R = COOEt)

250 mg (0.77 mmol) 3-(2,2,3,3,3-pentafluoropropoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid were dissolved in 25 ml of ethanolic HCl and stirred for 3 days. Removal of the solvent *in vacuo* afforded the title ester.

Yield: 0.25 g (92 %); MS 352 (M^+)

Preparation 9: Methyl 7-Hydroxy-4-methyl-2-oxo-2H-benzo[b]pyran-6-carboxylate (R = H)



A solution of 30 g (0.18 mol) methyl 2,4 dihydroxybenzoate and 26 g (0.2 mol) ethyl 3-oxobutanoate in 400 ml 75 % aqueous sulfuric acid was stirred for 2 h at room temperature. The reaction mixture was poured onto 500 g ice. After 1 h the resulting crystalls were collected by filtered and dried *in vacuo* to give the title coumarin.

Yield: 28 g (67 %); MS 234 (M^+)

The following intermediate was prepared in the same manner:

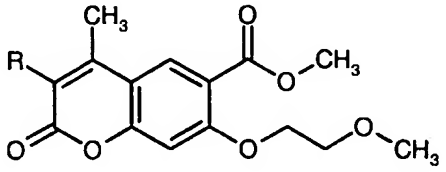
Preparation 9a

Methyl 3,4-Dimethyl-7-hydroxy-2-oxo-2H-benzo[b]pyran-6-carboxylate (R = CH_3)

from 30 g (0.18 mol) methyl 2,4 dihydroxybenzoate and 38.6 g (0.27 mmol) ethyl 2-acetylpropanoate for 24 h at room temperature;

Yield: 28 g (61 %); MS 248 (M^+)

<u>Preparation 10</u>: Methyl 7-(2-Methoxyethoxy)-4-methyl-2-oxo-2H-benzo[b]pyran-6-carboxylate (R = H)



A mixture of 28 g (0.12 mol) methyl 7-hydroxy-4-methyl-2-oxo-2H-benzo[b]pyran-6-carboxylate and 33.2 g (0.24 mol) potassium carbonate in 300 ml dry DMF was warmed to 80 °C and treated with 20 g (0.14 mol) 2-methoxyethyl bromide within 10 minutes. After keeping the reaction mixture at this temperature for 7 h it was cooled to room temperature, and the solids were removed by filtration. It was washed with ethanol, and the filtrate was concentrated under reduced pressure. The resulting yellow

solid was vigorously stirred with 30 ml ethanol, filtered, and dried *in vacuo* to afford the title compound.

Yield: 18.2 g (52 %); MS 292 (M^+)

The following intermediate was prepared in a similar manner:

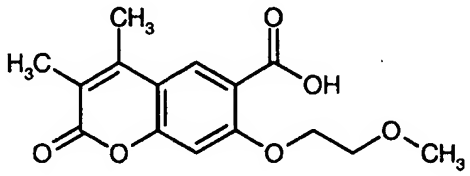
Preparation 10a

Methyl 3,4-Dimethyl-7-(2-methoxyethoxy)-2-oxo-2H-benzo[b]pyran-6-carboxylate (R = CH_3)

It was prepared from 1.62 g (6.53 mmol) methyl 3,4-dimethyl-7-hydroxy-2-oxo-2H-benzo[b]pyran-6-carboxylate, 3.6 g (26.1 mmol) potassium carbonate, and 998 mg (7.18 mmol) 2-methoxyethyl bromide. After 4 h at 80 °C the mixture was poured into 100 ml water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated *in vacuo*, and the title compound was purified by chromatography.

Yield: 1.18 g (62 %); MS 306 (M^+)

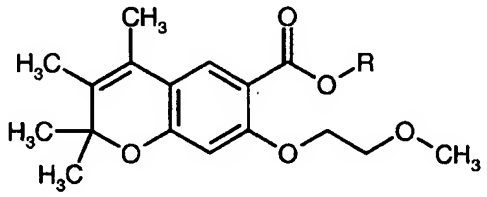
<u>Preparation 11</u>: 3,4-Dimethyl-7-(2-methoxyethoxy)-2-oxo-2H-benzo[b]pyran-6-carboxylic Acid



A solution of 0.86 g (2.94 mmol) methyl 3,4-dimethyl-7-(2-methoxyethoxy)-2-oxo-2H-benzo[b]pyran-6-carboxylate and 248 mg (4.41 mmol) potassium hydroxide in a mixture of 5 ml water and 7 ml ethanol was heated at 80 °C for 1 h. The solvents were removed *in vacuo*, and the remaining dark oil partioned between 5 % aqueous sulfuric acid and ether. The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure. The title compound was obtained by chromatography (silica gel, dichloromethane / ethanol 95:5).

Yield: 0.56 g (65 %); MS 292 (M^+)

Preparation 12: 7-(2-Methoxyethoxy)-2,2,3,4-tetramethyl-2H-benzo[b]pyran-6-carboxylic Acid (R = H)



A solution of 0.51 g (1.7 mmol) 3,4-dimethyl-7-(2-methoxyethoxy)-2-oxo-2H-benzo[b]pyran-6-carboxylic acid in 10 ml dry tetrahydrofuran was treated with 8.5 ml 1M methylmagnesium bromide in tetrahydrofuran at 0 °C. After stirring at room temperature for 10 min, the reaction mixture was heated at reflux for 20 min. It was concentrated under reduced pressure, and the remaining dark brown oil was partioned between 5 % aqueous sulfuric acid and ether. The organic layer was dried over sodium sulfate, the solvent removed *in vacuo*, and the title compound obtained by chromatography (silica gel, dichloromethane / ethanol 95:5).

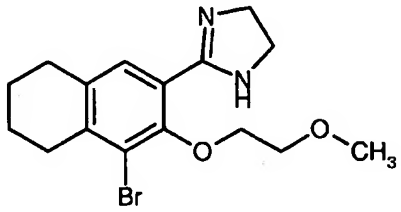
Yield: 337 mg (65 %); MS 306 (M^+)

Preparation 13: Propyl 7-(2-Methoxyethoxy)-2,2,3,4-tetramethyl-2H-benzo[b]pyran-6-carboxylate (R = C_3H_7)

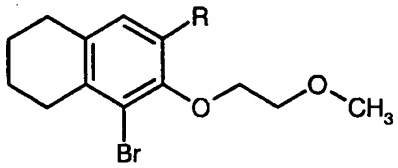
330 mg (1.07 mmol) 7-(2-methoxyethoxy)-2,2,3,4-tetramethyl-2H-benzo[b]pyran-6-carboxylic acid, 200 mg (1.29 mmol) 1,8-diaza-bicyclo[5.4.0]undec-7-ene, and 219 mg (1.29 mmol) propyl iodide were dissolved in 10 ml acetonitrile, and the mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the remaining dark brown oil was partioned between water and ethyl acetate. The organic layer was dried over sodium sulfate, the solvent removed *in vacuo*, and the title ester obtained by chromatography (silica gel, hexane / ethyl acetate 3:1).

Yield: 168 mg (45 %); MS 348 (M^+)

Example 1: 2-(4-Bromo-3-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole



Step A: 5-Bromo-6-(2-methoxyethoxy)-1,2,3,4-tetrahydronaphthalene (R = H)



5,6,7,8-Tetrahydronaphthalen-2-ol was brominated according to a known procedure (Acta Chem. Scand. 25 (1971), 94; Chem. Pharm. Bull. 39 (1991), 2896) to give a mixture of 1-bromo-5,6,7,8-tetrahydronaphthalen-2-ol and 3-bromo-5,6,7,8-tetrahydronaphthalen-2-ol in a ratio of 3:1. To a solution of 16.5 g (72.66 mmol) of the isomeric mixture in 220 ml dry DMF were added 8.22 g (73.25 mmol) potassium tert.-butoxide in several portions. After stirring for 1 h 6.85 g (72.46 mmol) 2-methoxyethyl chloride were added, and the mixture was heated at 85 °C for 4 h. It was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with water and brine, successively, dried over sodium sulfate, and concentrated under reduced pressure. It was chromatographed on silica gel with hexane / tert.-butylmethylether 10:1 to give 18.0 g (87 %) of a mixture of 5-bromo-6-(2-methoxyethoxy)-1,2,3,4-tetrahydronaphthalene and 6-bromo-7-(2-methoxyethoxy)-1,2,3,4-tetrahydronaphthalene in a ratio of 4:1.

Step B: 4-Bromo-3-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde (R = CHO)

5.4 g (18.9 mmol) of the mixture described in the previous step were dissolved in 45 ml dry dichloromethane. The solution was kept below 5 °C and vigorously stirred, while 5.8 g (30.6 mmol) titanium tetrachloride were added dropwise within 15 minutes. Within another 45 minutes 1.74 g (15.14 mmol) (dichloromethoxy)methane were added. The mixture was stirred for 2 h at room temperature and quenched by careful addition of 30 ml water. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, and concentrated *in vacuo*, and the title aldehyde was isolated from the residue by chromatography (silica gel, hexane / tert.-butylmethylether 10:1).
Yield: 0.64 g (13.5 %)

Step C: 4-Bromo-3-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (R = CN)

A mixture of 1.56 g (4.98 mmol) of the aldehyde from Step B, 0.62 g (8.92 mmol) hydroxylamine hydrochloride, and 0.73 g (8.9 mmol) sodium acetate in 8 ml dry ethanol were heated with reflux for 4 h. The solvent was removed *in vacuo*, and the residue was stirred with water followed by extraction with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude intermediate oxime was heated with 7.5 ml acetic anhydride at 100 °C for 4 h. The excess anhydride was removed *in vacuo*, and the residue treated with water and potassium carbonate to obtain a basic solution which was extracted with dichloromethane. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure, and the title nitrile was obtained by chromatography (silica gel, hexane / acetone 5:1).
Yield: 0.43 g (28 %)

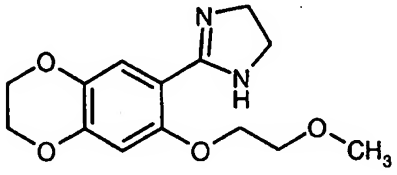
Step D: **2-(4-Bromo-3-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole**

A solution of 0.35 g (1.13 mmol) 4-bromo-3-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphthalene-2-carbonitrile in 8 ml dry ethanol was cooled to – 10 °C and saturated with gaseous hydrogen chloride within 30 minutes. After stirring overnight the solvent was removed under reduced pressure to leave the crude ethyl carboximidate, which was redissolved in 10 ml dry ethanol. 0.1 g (1.66 mmol) of 1,2-diaminoethane were added, and the mixture was stirred overnight, evaporated, and the title imidazoline was purified by chromatography (silica gel, dichloromethane / ethanol 8:1 to 4:1). It crystallized by stirring with hexane, was collected by filtration, and dried *in vacuo*.

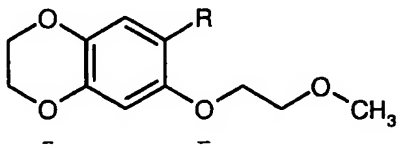
Yield: 0.07 g (17.5 %); beige crystalline solid, m.p. 94-96 °C; MS 352 and 354 (M^+)

The following two Examples were prepared by a similar sequence of steps using the same methods as set forth in **Example 1**:

Example 2: **2-(7-(2-Methoxyethoxy)-2,3-dihydro-benzo[1,4]dioxin-6-yl)-4,5-dihydro-1H-imidazole**



Step A: **6-(2-Methoxyethoxy)-2,3-dihydro-benzo[1,4]dioxine (R = H)**



2,3-Dihydro-benzo[1,4]dioxin-6-ol was prepared by oxidation of 6-acetyl-2,3-dihydro-benzo[1,4]dioxine (Tetrahedron 51 (1995), 3197), and 6.6 g (43.4 mmol) of this compound were alkylated with 4.06 g (42.94 mmol) 2-methoxyethyl chloride. After stirring overnight at 85 °C another 0.5 equiv. of the ethyl chloride and of potassium tert.-butoxide were added, and the reaction was continued for another day. The title compound was obtained as an oil and used for the next step without further chromatographic purification.

Yield: 8.3 g (91 %)

Step B: **7-(2-Methoxyethoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde (R = CHO)**

The intermediate aldehyde was prepared from 7.0 g (33.3 mmol) 6-(2-methoxyethoxy)-2,3-dihydro-benzo[1,4]dioxine, 3.05 g (26.55 mmol) (dichloromethoxy)methane, and 10.22 g (53.87 mmol) titanium tetrachloride, and it was purified by chromatography (silica gel, dichloromethane / ethanol 20:1).

Yield: 3.2 g (51 %); m.p. 84-85 °C; MS 238 (M^+)

Step C: **7-(2-Methoxyethoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carbonitrile (R = CN)**

The nitrile was prepared from 2.6 g (10.9 mmol) of the aldehyde in the manner described before. Heating was continued overnight, and the crystalline intermediate oxime was collected by filtration. The title compound was used for the next step

without further chromatographic purification. An analytical sample was obtained with dichloromethane / hexane 2:1 on silica gel.

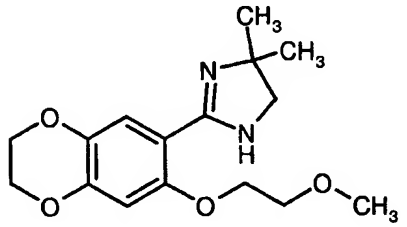
Yield: 2.5 g (97 %); m.p. 98-99 °C; MS 235 (M^+)

Step D: 2-(7-(2-Methoxyethoxy)-2,3-dihydro-benzo[1,4]dioxin-6-yl)-4,5-dihydro-1H-imidazole

The imidazoline was prepared from 0.3 g (1.27 mmol) 7-(2-methoxyethoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carbonitrile and 114 mg (1.9 mmol) 1,2-diaminoethane, purified by chromatography (silica gel, dichloromethane / ethanol 8:1 to 4:1), and crystallized by stirring with tert.-butylmethylether.

Yield: 0.08 g (23 %); colorless crystals, m.p. 77-78 °C; MS 278 (M^+)

Example 3: 4,4-Dimethyl-2-(7-(2-methoxyethoxy)-2,3-dihydro-benzo[1,4]dioxin-6-yl)-4,5-dihydro-1H-imidazole Hydrochloride

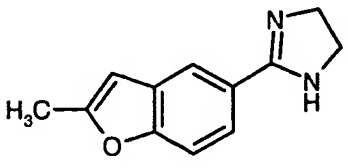


HCl

The title compound was prepared from 0.82 g (3.5 mmol) of the nitrile and 0.47 g (5.33 mmol) 1,2-diamino-2-methylpropane and chromatographed with dichloromethane / ethanol 91:9 to 80:20.

Yield: 0.28 g (23 %); colorless crystals, m.p. 162-164 °C; MS 306 (M^+)

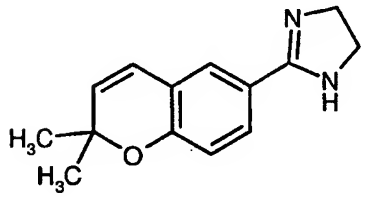
Example 4: 2-(2-Methylbenzofuran-5-yl)-4,5-dihydro-1H-imidazole



A solution of 2.0 g (12.7 mmol) 2-methylbenzofuran-5-carbonitrile (prepared according to a procedure from J. Heterocyclic Chem. 4 (1967), 441; Tetrahedron Lett. 1967, 2867) in 70 ml dry ethanol was saturated with hydrogen chloride by adding the gas for about 1 h and stirred over night at room temperature. It was concentrated under reduced pressure to leave the crude ethyl carboximidate. The intermediate was heated at reflux for 4 h with 8 ml 1,2-diaminoethane, and the title compound precipitated from the mixture after cooling to room temperature. The excess of diamine was removed *in vacuo*, and the residue was stirred with a small amount of water, filtered with suction, and dried.

Yield: 0.1 g (4 %); colorless crystals, m.p. 147 °C; MS 201 (M^++1)

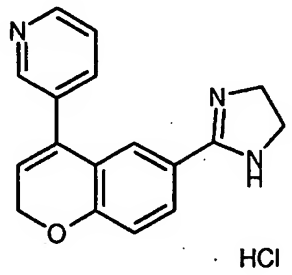
Example 5: 2-(2,2-Dimethyl-2H-benzo[b]pyran-6-yl)-4,5-dihydro-1H-imidazole



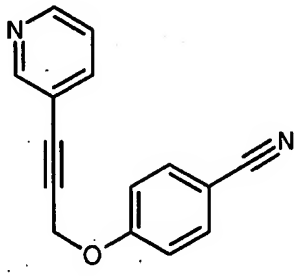
The intermediate 2,2-dimethyl-2H-benzo[b]pyran-6-carbonitrile was prepared according to a known procedure (J. Org. Chem. 37 (1972), 841; J. Med. Chem. 33 (1990), 492). The title imidazoline was prepared from 7.41 g (40.0 mmol) of the nitrile in the same manner as described for the previous Example.

Yield: 2.9 g (32 %); pale yellow powder, m.p. 152 °C; MS 229 (M^++1)

Example 6: 2-(4-(Pyridin-3-yl)-2H-benzo[b]pyran-6-yl)-4,5-dihydro-1H-imidazole Hydrochloride



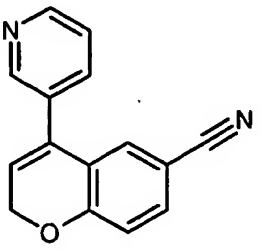
Step A: 4-(3-(Pyridin-3-yl)prop-2-ynyloxy)benzonitrile



4-(Prop-2-ynyloxy)benzonitrile was prepared from 4-hydroxybenzonitrile and propargyl bromide according to a procedure from J. Org. Chem. 37 (1972), 841. A mixture of 16.7 g (106.3 mmol) of the alkyne, 21.7 g (105.9 mmol) 3-iodopyridine, 1.52 g (2.17 mmol) $Pd(PPh_3)_2Cl_2$, 1.13 g (5.93 mmol) Cu(I) iodide, and 160 ml triethylamine was heated at 90 – 95 °C for 5 h in an autoclave. After cooling it was diluted with dichloromethane and extracted with water. The organic layer was washed two times with water, dried over sodium sulfate, and concentrated under reduced pressure. The title compound was obtained by chromatography on silica gel with hexane / ethanol gradient 3:1 to 3:2 and solidified by stirring with ethanol.

Yield: 12.8 g (52 %); beige crystalline solid

Step B: **4-(Pyridin-3-yl)-2H-benzo[b]pyran-6-carbonitrile**



A mixture of 12.8 g (54.64 mmol) of the alkyne from the previous step and 250 ml Dowtherm A was heated for 8 h at 250 °C. After cooling it was diluted with tert.-butylmethylether and 1N hydrochloric acid, and the organic layer was washed with 1N hydrochloric acid. The combined aqueous layers were adjusted to pH11 with 2N NaOH followed by two extractions with chloroform. The extracts were combined, dried over sodium sulfate, concentrated under reduced pressure, and the title benzopyran was isolated from the residue as a pale yellow oil by chromatography (silica gel, dichloromethane / ethanol 97:3), from which a fraction of a beige crystalline solid was obtained by stirring with ethyl acetate / ether.

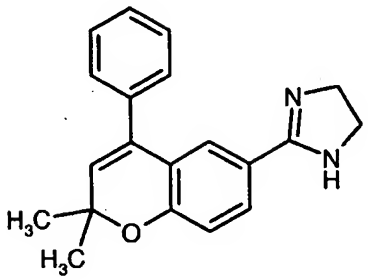
Total yield: 0.63 g (5 %)

Step C: **2-(4-(Pyridin-3-yl)-2H-benzo[b]pyran-6-yl)-4,5-dihydro-1H-imidazole Hydrochloride**

A solution of 0.63 g (2.7 mmol) of the nitrile from Step B in 40 ml dry ethanol was cooled with ice, saturated with hydrogen chloride, and stirred overnight at room temperature. It was concentrated under reduced pressure to leave the crude ethyl carboximidate, which was redissolved in 15 ml dry ethanol followed by addition of 0.32 g (5.32 mmol) 1,2-diaminoethane. The mixture was heated with reflux for 2.5 h, concentrated *in vacuo*, and the title imidazoline was obtained from the residue by chromatography (silica gel, dichloromethane / methanol 3:1). It was dissolved in a small amount of ethanol and treated with HCl in ether to give the title hydrochloride, which was collected by filtration, and dried *in vacuo*.

Yield: 0.15 g (18 %); beige crystalline solid, m.p. > 293 °C (dec.)

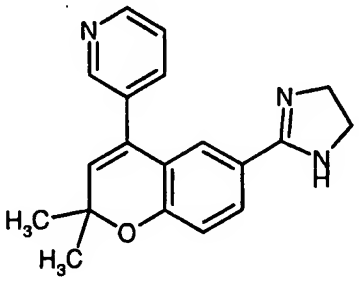
Example 7: 2-(2,2-Dimethyl-4-phenyl-2H-benzo[b]pyran-6-yl)-4,5-dihydro-1H-imidazole



The intermediate 2,2-dimethyl-4-phenyl-2H-benzo[b]pyran-6-carbonitrile was prepared by Pd-catalyzed coupling between iodobenzene and 4-(1,1-dimethylprop-2-ynyloxy)benzonitrile followed by thermal cyclization according to a known procedure from Eur. Pat. Appl. EP 298452. The title imidazoline was prepared from 0.3 g (1.15 mmol) of the nitrile as described in the previous Example. It was purified by chromatography (silica gel, dichloromethane / methanol 7:3 followed by methanol) and recrystallized from ethyl acetate.

Yield: 0.08 g (23 %); beige crystalline solid, m.p. 167-169 °C

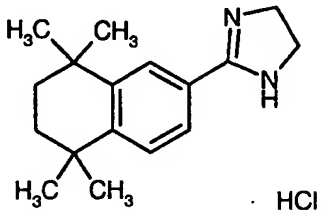
Example 8: 2-(2,2-Dimethyl-4-(pyridine-3-yl)-2H-benzo[b]pyran-6-yl)-4,5-dihydro-1H-imidazole



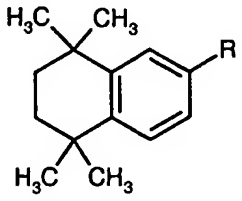
The intermediate 2,2-dimethyl-4-(pyridin-3-yl)-2H-benzo[b]pyran-6-carbonitrile was prepared according to known methods (Bioorg. Med. Chem. Lett. 2 (1992), 381; Eur. Pat. Appl. EP 298452). A mixture of 1.0 g (3.81 mmol) of the nitrile and 1.02 g (4.39 mmol) ethylendiamine tosylate was heated with melting at 220 °C for 90 minutes. It was dissolved in hot ethanol. The excess of tosylate precipitated upon cooling, was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was treated with water followed by three extractions with ethyl acetate. The aqueous layer was brought to pH11 with 2N sodium hydroxide and extracted three times with tert.-butylmethylether. The combined extracts were dried over sodium sulfate, and concentrated *in vacuo* to leave a beige residue from which the title imidazoline was obtained by chromatography (silica gel, dichloromethane / methanol 1:1) and recrystallized from ether.

Yield: 0.37 g (32 %); beige crystalline solid, m.p. 166-169 °C

Example 9: 2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydrochloride



Step A: 5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (R = COOH)



To a mixture of 5.8 g (0.145 mol) sodium hydroxide and 20.2 g (0.1 mol) 1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene in 80 ml pyridine were added at 90 – 100 °C 37.8 g (0.24 mmol) potassium permanganate in small portions. After stirring at 95 °C for 2 h the mixture was cooled to room temperature, filtered, and carefully acidified with conc. hydrochloric acid. The mixture was extracted with ethyl acetate, and the extract was dried over sodium sulfate, and concentrated *in vacuo* to give 13.6 g (58 %) of the crystalline acid; m.p. 142 °C.

Step B: Ethyl 5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (R = COOEt)

A solution of 12 g (50 mmol) of 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid in 200 ml dry ethanol and 20 ml conc. sulfuric acid was heated at reflux for 10 h. The mixture was cooled to room temperature, treated with water (500 ml), and neutralized with sodium bicarbonate. It was extracted with ethyl acetate, and the extract was dried over sodium sulfate and concentrated under reduced pressure to give the title ester.

Yield: 10 g (76%); pale yellow crystals, m.p. 98 °C

Step C: 2-Aminoethyl 5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carboxamide (R = $CONHCH_2CH_2NH_2$)

A mixture of 10 g (38 mmol) of the ester from the previous step and 23 g (38 mmol) ethylenediamine was heated for 6 h at 100°C. After cooling to room temperature water (500 ml) was added. The precipitate of the title compound was collected by filtration, washed with water, and dried *in vacuo*.

Yield: 8 g (76 %); amorphous solid

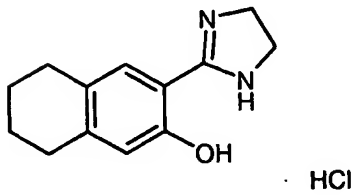
Step D: 2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydrochloride

To 2 g (7.3 mmol) of the amide from Step C was added carefully an excess of $POCl_3$, and the mixture was heated for 5 h at 80-90 °C. After evaporation it was poured into

ice-water and made basic with 5 N NaOH. It was extracted with dichloromethane. The extract was washed with water, dried over sodium sulfate, concentrated *in vacuo*, and chromatographed with dichloromethane / ethanol 7:3 on silica gel to give the title imidazoline which was converted to its hydrochloride salt.

Yield: 1.05 g (51 %); beige amorphous solid, m.p. 239-243 °C

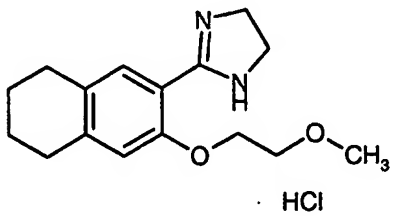
Example 10: 3-(4,5-Dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydronaphthalen-2-ol Hydrochloride



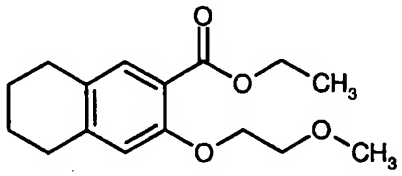
A mixture of 4.4 g (20 mmol) of ethyl 3-hydroxy-5,6,7,8 tetrahydronaphthalene-2-carboxylate (prepared according to J. Chem. Soc. C 1968, 2836) and 5.35 g (23 mmol) 1,2-diaminoethane monotosylate was heated for 2 hours at 220°C. After cooling to room temperature 100 ml of water were added, and the precipitate of the crude title imidazoline was collected by filtration and chromatographed with dichloromethane / ethanol 9:1 on silica gel.

Yield: 1.7 g (33 %); beige crystalline solid

Example 11: 2-(3-(2-Methoxyethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydrochloride



Step A: Ethyl 3-(2-Methoxyethoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate



To a solution of 13.2 g (60 mmol) of ethyl 3-hydroxy-5,6,7,8 tetrahydronaphthalene-2-carboxylate in 60 ml dry DMF were added 6.8 g (60 mmol) potassium tert.-butoxide and 5.67 g (60 mmol) 2-methoxyethyl chloride. The mixture was heated at 85 °C for 18 hours. After cooling to room temperature it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give 12.6 g (75 %) of the title compound as a syrup.

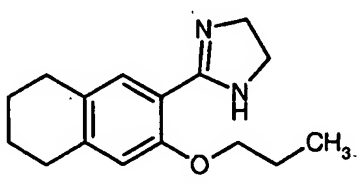
Step B: 2-(3-(2-Methoxyethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydrochloride

The imidazoline was prepared from 2 g (7.2 mmol) of the ester from Step A and 4.3 g (7.2 mmol) 1,2-diaminoethane monotosylate as described in the previous Example. It was purified by chromatography on silica gel with dichloromethane / ethanol 8:1.

Yield: 0.3 g (15 %); beige amorphous solid, m.p. 74 °C

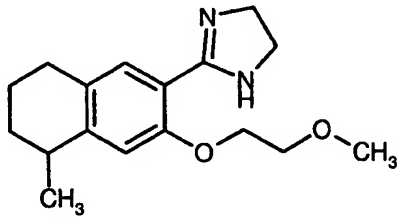
The following Example was prepared in the same manner as **Example 11**:

Example 12: 2-(3-Propoxy-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole



beige crystalline material.

Example 13: 2-(3-(2-Methoxyethoxy)-5-methyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole

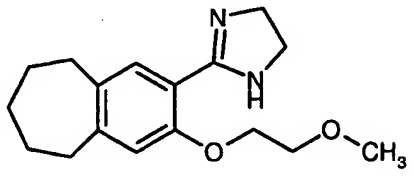


To a solution of 90 mg (0.29 mmol) 2-aminoethyl 3-(2-methoxyethoxy)-5-methyl-5,6,7,8-tetrahydronaphthyl-2-carboxamide in 5 ml dry dichloromethane were added 290 mg (0.88 mmol) diethylaminomethyl-polystyrene and 0.126 ml (0.88 mmol) trimethylsilyl iodide. The mixture was stirred for 48 h at room temperature, and the resin was filtered and washed with dichloromethane and ethanol, successively. After removal of the solvent under reduced pressure chromatography on silica gel with dichloromethane / 10% ethanolic ammonia 95:5 afforded the title imidazoline.

Yield: 60 mg (71 %); beige crystalline solid, m.p. 60-61 °C; MS 288 (M^+)

The following Examples were prepared in the same manner as **Example 11**:

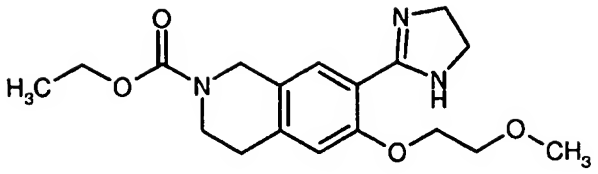
Example 14: 2-(3-(2-Methoxyethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-4,5-dihydro-1H-imidazole



from 140 mg (0.46 mmol) of 2-aminoethyl 3-(2-methoxyethoxy)-6,7,8,9-tetrahydro-5H-benzocycloheptene-2-carboxamide, 0.195 ml (1.37 mmol) trimethylsilyl iodide, and 458 mg (1.37 mmol) diethylaminomethyl-polystyrene for 16 h at room temperature;

Yield: 93 mg (71 %); beige resin; MS 288 (M^+)

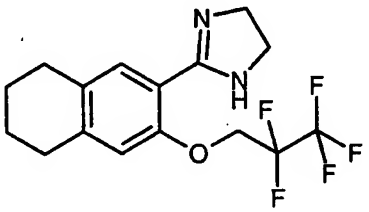
Example 15: Ethyl 7-(4,5-Dihydro-1H-imidazol-2-yl)-6-(2-methoxyethoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylate



from 40 mg (0.11 mmol) 2-aminoethyl 2-ethoxycarbonyl-6-(2-methoxyethoxy)-3,4-dihydro-1H-isoquinoline-7-carboxamide, 110 mg (0.33 mmol) diethylaminomethyl-polystyrene, and 0.047 ml (0.33 mmol) trimethylsilyl iodide for 64 h at room temperature;

Yield: 16 mg (42 %); pale yellow oil; MS 347 (M^+)

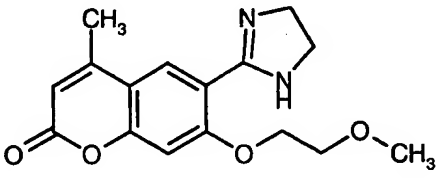
Example 16: 2-(3-(2,2,3,3,3-Pentafluoropropoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole



from 110 mg (0.30 mmol) 2-aminoethyl 3-(2,2,3,3,3-pentafluoropropoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxamide, 300 mg (0.90 mmol) diethylaminomethyl-polystyrene, and 0.129 ml (0.90 mmol) trimethylsilyl iodide;

Yield: 70 mg (67 %); pale yellow resin; MS 348 (M^+)

Example 17: 2-(7-(2-Methoxyethoxy)-4-methyl-2-oxo-2H-benzo[b]pyran-6-yl)-4,5-dihydro-1H-imidazole

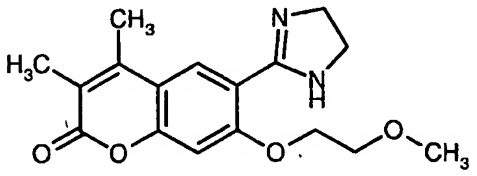


from 7.3 g (22.8 mmol) 2-aminoethyl 7-(2-methoxyethoxy)-4-methyl-2-oxo-2H-benzo[b]pyran-6-carboxamide with 23.3 g (70.0 mmol) diethylaminomethyl-

polystyrene resin and 10 ml (70.0 mmol) trimethylsilyl iodide in 300 ml dry dichloromethane for 18 h at room temperature;

Yield: 4.40 g (64 %); pale yellow crystals, m.p. 150-152 °C; MS 302 (M^+)

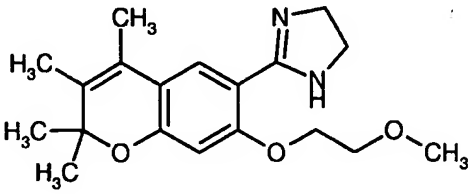
Example 18: 2-(3,4-Dimethyl-7-(2-methoxyethoxy)-2-oxo-2H-benzo[b]pyran-6-yl)-4,5-dihydro-1H-imidazole



from 0.23 g (0.69 mmol) 2-aminoethyl 3,4-dimethyl-7-(2-methoxyethoxy)-2-oxo-2H-benzo[b]pyran-6-carboxamide with 690 mg (2.07 mmol) diethylaminomethyl-polystyrene resin and 0.294 ml (2.07 mmol) trimethylsilyl iodide in 10 ml dry dichloromethane for 3 days at room temperature;

Yield: 0.11 g (51 %); colorless crystals, m.p. 174-176 °C; MS 316 (M^+)

Example19: 2-(7-(2-Methoxyethoxy)-2,2,3,4-tetramethyl-2H-benzo[b]pyran-6-yl)-4,5-dihydro-1H-imidazole Hydroiodide



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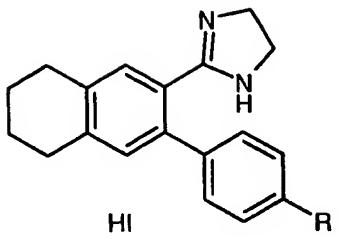
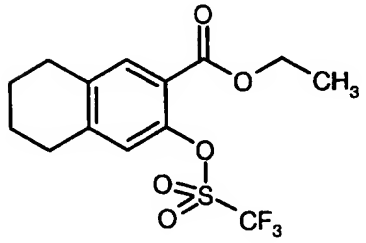
from 60 mg (0.17 mmol) 2-aminoethyl 7-(2-methoxyethoxy)-2,2,3,4-tetramethyl-2H-benzo[b]pyran-6-carboxamide with 172 mg (0.52 mmol) diethylaminomethyl-polystyrene resin and 0.074 ml (0.52 mmol) trimethylsilyl iodide in 10 ml dry dichloromethane for 7 days at room temperature;

Example 20: 2-(3-Phenyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydroiodide (R = H)



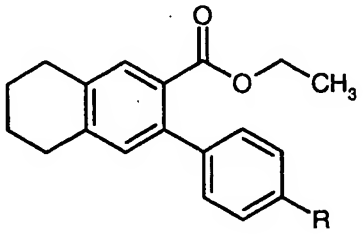
Step A: Ethyl 3-Trifluoromethylsulfonyloxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate



A stirred solution of 2.2 g (10 mmol) of ethyl 3-hydroxy-5,6,7,8 tetrahydronaphthalene-2-carboxylate (prepared according to J. Chem. Soc. C 1968, 2836), 1.58 g (20 mmol) of pyridine, and 20 mg of 4-dimethylaminopyridine (DMAP) in 100 ml of dry dichloromethane was cooled to -1 °C followed by careful addition of 5.6 g (20 mmol) of triflic anhydride, while the temperature was kept below 2 °C. The mixture was slowly brought to ambient temperature and stirring was continued for 16 h. Another amount of pyridine (3 ml) and 10 mmol of triflic anhydride was added, and it was stirred for another 6 h, until the reaction was complete as detected by TLC (hexane / ethyl acetate 98:2). The mixture was poured on to crushed ice, and the aqueous layer was separated and extracted twice with dichloromethane. The combined extracts were washed twice with water, dried over sodium sulfate, and concentrated to dryness. The residue was filtered through a plug of 15 g of silica gel with dichloromethane and concentrated *in vacuo*.

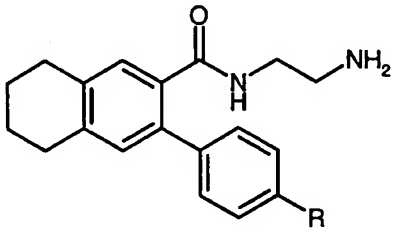
Yield: 3.16 g (90 %); yellow oil

Step B: **Ethyl 3-Phenyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (R = H)**



To a solution of 0.6 g (1.7 mmol) of the triflate in 10 ml of oxygen-free dioxane were added 0.244 g (2.0 mmol) of benzeneboronic acid, 0.1g (0.085 mmol) of $Pd(PPh_3)_4$, 1.8 g (8.5 mmol) potassium phosphate, and 0.46 g (25.5 mmol) water, while argon was bubbled through the solution for five minutes. The vessel was sealed and heated at 100 °C for 4 h. After cooling the mixture was poured on to crushed ice, and the aqueous layer was separated and extracted twice with dichloromethane. The combined extracts were washed three times with water, dried over sodium sulfate, and concentrated under reduced pressure. The title intermediate was purified by flash chromatography on silica gel with an i-hexane / ethyl acetate gradient (100 to 97:3). Yield: 0.24 g (50 %); colorless oil; MS 280 (M^+)

Step C: **2-Aminoethyl 3-Phenyl-5,6,7,8-tetrahydronaphthalene-2-carboxamide (R = H)**



A solution of 0.24 g (0.85 mmol) of the ester from the previous step and 15.3 mg (0.85 mmol) water in 4 ml neat ethylenediamine (EDA) was stirred at 100 °C, until the reaction was nearly complete (after 3 days) as detected by TLC (dichloromethane / ethanolic ammonia 9:1). After cooling the mixture was diluted with toluene and the excess EDA and water were removed azeotropically. The title amide was obtained from the residue via flash chromatography on silica gel using a dichloromethane / ethanolic ammonia gradient 100 to 90:10.

Yield: 203 mg (81 %); yellow powder; MS 295.3 (M^++1)

Step D: 2-(3-Phenyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydroiodide (R = H)

To a solution of 0.2 g (0.68 mmol) of the aminoethyl amide in 7 ml dichloromethane were added 3 equivalents of diethylaminomethyl-polystyrene and 40 mg (0.2 mmol) of trimethylsilyl iodide. The mixture was stirred at room temperature for 3 days. Another two equivalents of base and TMS iodide were added, stirring was continued, and after 7days the reaction was nearly complete as detected by TLC (dichloromethane / ethanolic ammonia 4:1). The resin was removed by filtration and thoroughly rinsed with dichloromethane and methanol. The combined filtrates were concentrated under reduced pressure, and the residue was purified via prep. HPLC on RP-18 silica gel using an acetonitrile / water gradient.

Yield: 118 mg (43 %); yellow oil; MS 277.2 (M^++1)

The following Examples **21, 22,** and **23,** were prepared in the same manner as **Example 20** using the corresponding benzeneboronic acids:

Example 21: 2-(3-(4-Methylphenyl)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydroiodide (R = CH_3)

Step A: Ethyl 3-(4-Methylphenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (R = CH_3)

Yield: 0.32 g (64 %); colorless oil; MS 295.2 (M^++1)

Step B: 2-Aminoethyl 3-(4-Methylphenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide (R = CH_3)

Yield: 0.27 g (81 %); yellow oil

Step C: 2-(3-(4-Methylphenyl)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydroiodide (R = CH_3)

The reaction was complete after 10 days at room temperature.

Yield: 165 mg (45 %); yellow oil; MS 291.0 (M^++1)

Example 22: 2-(3-(4-Methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydroiodide (R = OCH_3)

Step A: Ethyl 3-(4-Methoxyphenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (R = OCH_3)

Yield: 0.40 g (76 %); colorless oil; MS 311.1 (M^++1)

Step B: 2-Aminoethyl 3-(4-Methoxyphenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide (R = OCH_3)

Yield: 0.24 g (57 %); yellow oil

Step C: 2-(3-(4-Methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydroiodide (R = OCH_3)

The reaction was complete after 11 days at room temperature.

Yield: 12.9 mg (4 %); yellow oil; MS 307.2 (M^++1)

Example 23: 2-(3-(4-Chlorophenyl)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydroiodide (R = Cl)

Step A: Ethyl 3-(4-Chlorophenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (R = Cl)

Yield: 0.50 g (94 %); colorless oil; MS 315.2 (M^++1)

Step B: 2-Aminoethyl 3-(4-Clorophenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide (R = Cl)

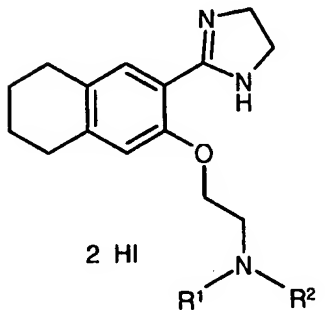
Yield: 0.37 g (71 %); yellow powder; MS 329.1 (M^++1)

Step C: 2-(3-(4-Chlorophenyl)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Hydroiodide (R = Cl)

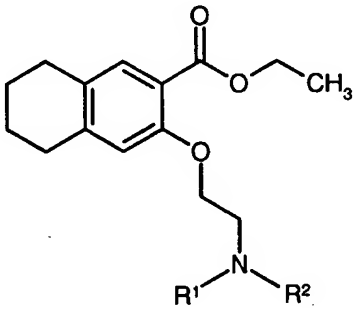
The reaction was complete after 7 days at room temperature.

Yield: 148 mg (30 %); yellow oil; MS 311.0 and 313.0 (M^++1)

Example 24: 2-(3-(2-(N,N-Dimethylamino)ethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Dihydroiodide ($R^1 = R^2 = CH_3$)



Step A: Ethyl 3-(2-(N,N-Dimethylamino)ethoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate ($R^1 = R^2 = CH_3$)

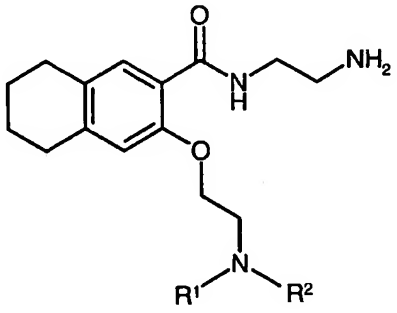


A stirred mixture of 1 g (4.54 mmol) of ethyl 3-hydroxy-5,6,7,8 tetrahydronaphthalene-2-carboxylate (prepared according to J. Chem. Soc. C 1968, 2836), 0.98 g (6.81 mmol) of (2-chloroethyl)dimethyl amine hydrochloride, and 1.88 g (13.6 mmol) of anhydrous potassium carbonate in 8 ml of dry DMF was heated at 85 °C for 16 h. After addition of another 0.37 g (2.7 mmol) of carbonate and 0.2 g (1.39 mmol) of alkyl chloride stirring was continued for the same time until the reaction was complete as detected by TLC (i-hexane / acetone 9:1). The mixture was poured into water (30 ml), and the aqueous layer extracted three times with ethyl

acetate. The combined extracts were washed twice with water, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified via flash chromatography on silica gel using an i-hexane / acetone gradient 100 to 40:60 to give the title intermediate.

Yield: 0.49 g (37 %); brownish oil

Step B: 2-Aminoethyl 3-(2-(N,N-Dimethylamino)ethoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxamide ($R^1 = R^2 = CH_3$)



A mixture of 0.49 g (1.68 mmol) of the ester from the previous step, 8 ml neat ethylenediamine (EDA), and 30.3 mg (1.68 mmol) water was heated at 100 °C for 24 h. The excess of EDA was removed *in vacuo*, and the evaporation was repeated after dilution with toluene. The residue was coated on silica gel and purified via flash chromatography using a dichloromethane / ethanolic ammonia gradient 100 to 90:10 as an eluent.

Yield: 0.22 g (43 %); yellow oil

Step C: 2-(3-(2-(N,N-Dimethylamino)ethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Dihydroiodide ($R^1 = R^2 = CH_3$)

To a solution of 0.22 g (0.72 mmol) of the amide from the previous step in 7 ml dichloromethane were added 3 equivalents of diethylaminomethyl-polystyrene, and 0.44 g (2.2 mmol) of trimethylsilyl iodide. The mixture was stirred at ambient temperature for 6 d until the reaction was nearly complete as detected by TLC

(dichloromethane /ethanolic ammonia 9:1). The resin was removed by filtration, thoroughly rinsed with dichloromethane and ethanol, and the combined filtrates were concentrated *in vacuo*. The residue was purified via prep. HPLC on RP-18 silica gel using an acetonitrile / water gradient to give the title imidazoline.

Yield: 66.5 mg (17 %); yellow oil which solidified upon standing; MS 288.1 (M^++1)

The following Examples **25** and **26** were prepared in the same manner as **Example 24** starting with the corresponding 2-chloroethylamine hydrochlorides:

Example 25: 2-(3-(2-(Morpholin-4-yl)ethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Dihydroiodide (R^1 - R^2 = $-CH_2CH_2OCH_2CH_2-$)

Step A: Ethyl 3-(2-(Morpholin-4-yl)ethoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (R^1 - R^2 = $-CH_2CH_2OCH_2CH_2-$)

Yield: 0.92 g (61 %); yellow oil

Step B: 2-Aminoethyl 3-(2-(Morpholin-4-yl)ethoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxamide (R^1 - R^2 = $-CH_2CH_2OCH_2CH_2-$)

Yield: 0.91 g (95 %); yellow oil

Step C: 2-(3-(2-(Morpholin-4-yl)ethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Dihydroiodide (R^1 - R^2 = $-CH_2CH_2OCH_2CH_2-$)

Yield: 0.46 g (30 %); yellow oil; MS 330.1 (M^++1)

Example 26: 2-(3-(2-(N,N-Diisopropylamino)ethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Dihydroiodide (R^1 = R^2 = $CH(CH_3)_2$)

Step A: Ethyl 3-(2-(N,N-Diisopropylamino)ethoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (R^1 = R^2 = $CH(CH_3)_2$)

Yield: 0.85 g (54 %); yellow oil

Step B: **2-Aminoethyl 3-(2-(N,N-Diisopropylamino)ethoxy)-5,6,7,8-tetrahydronaphthalene-2-carboxamide ($R^1 = R^2 = CH(CH_3)_2$)**

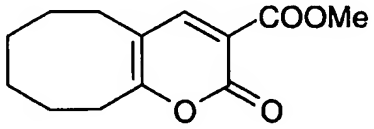
Yield: 0.77 g (87 %); brownish oil

StepC:2-(3-(2-(N,N-Diisopropylamino)ethoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1H-imidazole Dihydroiodide ($R^1 = R^2 = CH(CH_3)_2$)

Yield: 0.23 g (18 %); yellow oil; MS 344.3 (M^++1)

Example 27

Methyl 2-oxo-5,6,7,8,9,10-hexahydro-cycloocta[b]-2H-pyran-3-carboxylate

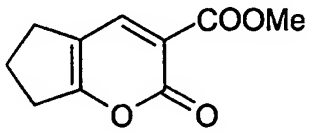


The primary addition product obtained from 686 mg (5.45 mmol) cyclooctanone and 1.06 g (6.53 mmol) dimethy methoxymethylene malonate, prepared using the method generally described by **Preparation 2** was dissolved in 15 ml toluene and heated for 4 h in the presence of 0.3 equivalents toluene-4-sulfonic acid. After removal of the solvent the remaining brown oil was purified via chromatography (silica gel, ethyl acetate : hexane 1:2).

Yield: 57%; MS 236 (M^+)

Example 28

Methyl 2-oxo-6,7-dihydro-cyclopenta[b]-2H,5H-pyran-3-carboxylate



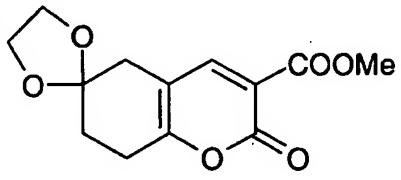
The primary addition product obtained from 1.07 g (12.71 mmol) cyclopentanone and 2.48 g (15.26 mmol) dimethy methoxymethylene malonate, prepared using the method

described by **Preparation 2,** was dissolved in 20 ml DMF and was heated to 150°C for 3 h in the presence of 2 g molecular sieves 0.3 nm. After filtration and removal of the solvent the remaining brown oil was purified via chromatography (silica gel, ethyl acetate : hexane 1:2).

Yield: 34%; MS 194 (M^+)

Example 29

Methyl 2-oxo-6-spiro-2'-(1',3')dioxolane-7,8-dihydro-1H,2H-1-benzo[b]pyran-3-carboxylate

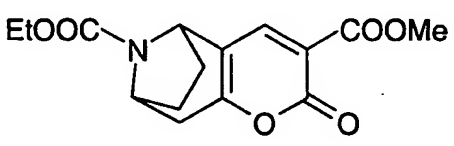


The primary addition product obtained from 850 mg (5.45 mmol) 1,4-cyclohexandione monoethylene ketal and 1.06 g (6.53 mmol) dimethy methoxymethylene malonate, prepared using the method of Preparation 2, was dissolved in 20 ml DMF and was heated to 150°C for 3 h in the presence of 2 g molecular sieves 0.3 nm. After filtration and removal of the solvent the remaining brown oil was purified via chromatography (silica gel, ethyl acetate : hexane 1:2).

Yield: 49%; MS 266 (M^+)

Example 30

Methyl 6-aza-5,7-ethano-6-(ethoxycarbonyl)-2-oxo-5,6,7,8-tetrahydro-2H-1-benzo[b]pyran-3-carboxylate

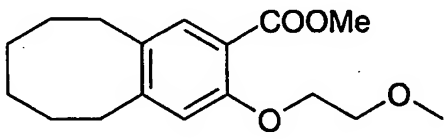


The primary addition product obtained from 1.46 g (7.42 mmol) tropinone and 1.44 g (8.90 mmol) dimethy methoxymethylene malonate, prepared using the method of Preparation 2, was dissolved in 30 ml toluene and heated for 4 h in the presence of 0.3 equivalents toluene-4-sulfonic acid. After removal of the solvent the remaining brown oil was purified via chromatography (silica gel, ethyl acetate : hexane 1:1).

Yield: 50%; MS 319 (M^+)

Example 31

Methyl 2-(2'-methoxy-ethoxy)-5,6,7,8,9,10-hexahydro-benzocyclooctene-3-carboxylate

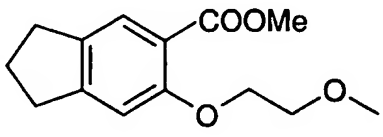


Intermediates for this example were prepared using the method described by **Preparation 3**. From heating 730 mg (3.09 mmol) methyl 2-oxo-5,6,7,8,9,10-hexahydro-cycloocta[b]-2H-pyran-3-carboxylate and 1.33 g (9.27 mmol) 1,1-bis-(2'-methoxy-ethoxy)-ethene in boiling xylene for 12 h the title compound was obtained after removal of the solvent and chromatographic purification with ethyl acetate / hexane 1: 1.

Yield: 56%; MS 291 (M^+)

Example 32

Methyl 2-(2'-methoxy-ethoxy)-6,7-dihydro-5H-benzocyclopentene-3-carboxylate



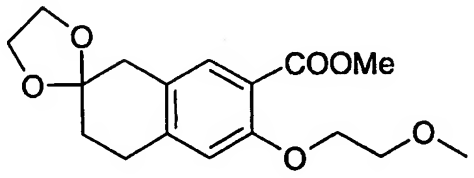
Intermediates for this example were prepared using the method described by **Preparation 3**. From heating 1.70 g (8.74 mmol methyl 2-oxo-6,7-dihydro-

cyclopenta[b]-2H,5H-pyran-3-carboxylate and 3.78 g (26.2 mmol) 1,1-bis-(2'-methoxy-ethoxy)-ethene in boiling xylene for 12 h the title compound was obtained after removal of the solvent and chromatographic purification with ethyl acetate / hexane 1: 1.

Yield: 48%; **MS 250 (M^+)**

Example 33

Methyl 6-(2'-methoxy-ethoxy)-2-spiro-2'-[1'',3'']dioxolane-3,4-dihydro-1H-naphthalene-7-carboxylate

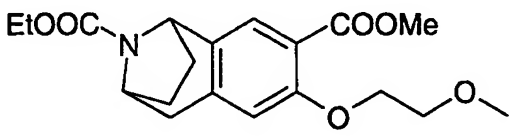


Intermediates for this example were prepared using the method described by **Preparation 3**. From heating 710 mg (2.66 mmol) methyl 2-oxo-6-spiro-2'-(1',3')dioxolane-7,8-dihydro-1H,2H-1-benzo[b]pyran-3-carboxylate and 961 mg (6.67 mmol) 1,1-bis-(2'-methoxy-ethoxy)-ethene in boiling xylene for 12 h the title compound was obtained after removal of the solvent and chromatographic purification with ethyl acetate / hexane 1: 1.

Yield: 21%; MS 322 (M^+)

Example 34

Methyl 1,3-ethano-2-(ethoxycarbonyl)-6-(2'-methoxy-ethoxy)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate



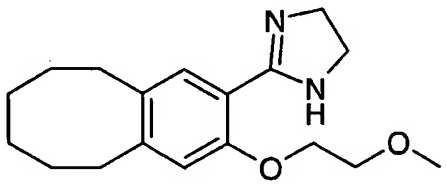
Intermediates for this example were prepared using the method described by **Preparation 3**. From heating 1.10 g (3.44 mmol) methyl 6-aza-5,7-ethano-6-(ethoxycarbonyl)-2-oxo-8-hydro-2H-1-benzo[b]pyran-3-carboxylate and 1.49 g (10.33 mmol) 1,1-bis-(2'-methoxy-ethoxy)-ethene in boiling xylene for 12 h the title compound was obtained after removal of the solvent and chromatographic purification with ethyl acetate / hexane 1: 1.

Yield: 23%; MS 363 (M^+)

The following compounds of **Examples 35, 36, 37,** and **38**are prepared utilizing the method as described by **Preparation 4** and the process substantially as described by **Examples 13 to 19**:

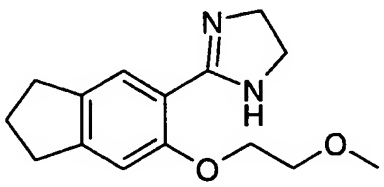
Example 35

2-(2'-(2''-methoxy-ethoxy)-5',6',7',8',9',10'-hexahydro-benzocyclooctene-3'-yl)-4,5-dihydro-1H-imidazole



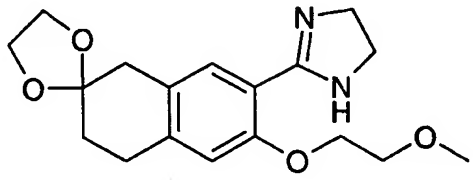
Example 36

2-(2'-(2''-methoxy-ethoxy)-6',7'-dihydro-5H-benzocyclopentene-3'-yl)-4,5-dihydro-1H-imidazole



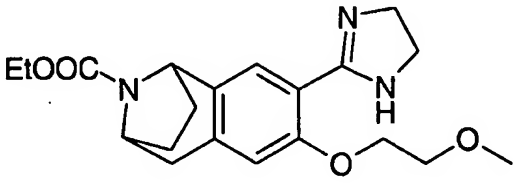
Example 37

2-(6'-(2''-methoxy-ethoxy)-2'-spiro-2'''-[1''',3''']dioxolane-3',4'-dihydro-1H-naphth-7'-yl)-4,5-dihydro-1H-imidazole

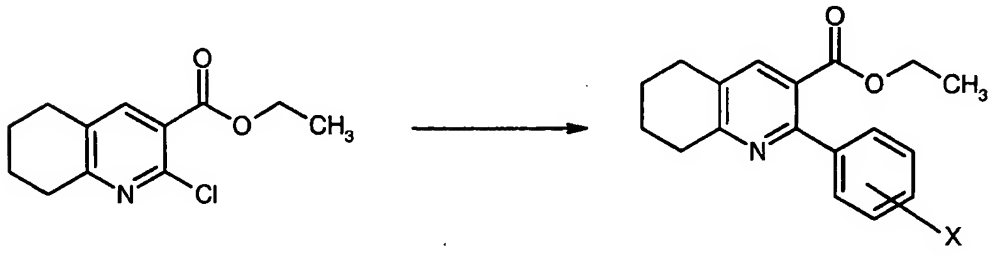


Example 38

2-(1',3'-ethano-2'(ethoxycarbonyl)-6'(2''methoxy-ethoxy)-1',2',3',4'-tetrahydroisoquinolin-7'-yl)-4,5-dihydro-1H-imidazole



General procedure for the Suzuki coupling reaction of ethyl 2-chloro-5,6,7,8-tetrahydro-quinoline-3-carboxylate with benzeneboronic acids



A solution of 5 mmol ethyl 2-chloro-5,6,7,8-tetrahydro-quinoline-3-carboxylate (prepared according to GB864208 [CA 61: 19957]), 0.5 mmol $Pd(PPh_3)_4$, and 10 mmol benzeneboronic acid in a mixture of 7.5 ml of 2M aqueous sodium carbonate

solution and 20 ml of dioxane was heated for 40 h to 80 °C. It was extracted with ethyl acetate, and the organic layer was dried and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with a dichloromethane / hexane gradient.

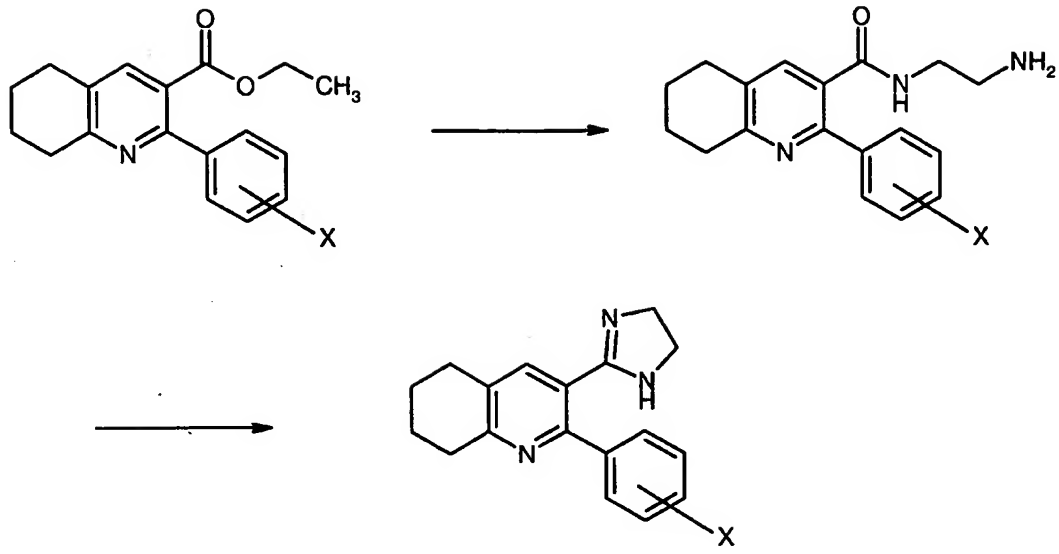
The following compounds were synthesized according to this procedure:

Ethyl 2-(3-Chlorophenyl)-5,6,7,8-tetrahydro-quinoline-3-carboxylate (X = 3-Cl)
from 1 g (4.17 mmol) ethyl 2-chloro-5,6,7,8-tetrahydro-quinoline-3-carboxylate and 1.32 g (8.34 mmol) (3-chlorobenzene)boronic acid;
yield: 450 mg (34 %); MS 315 (M^+)

Ethyl 2-(4-Methylphenyl)-5,6,7,8-tetrahydro-quinoline-3-carboxylate (X = 4-CH_3)
from 1 g (4.17 mmol) ethyl 2-chloro-5,6,7,8-tetrahydro-quinoline-3-carboxylate and 1.14 g (8.34 mmol) (4-methylbenzene)boronic acid;
yield: 520 mg (42 %); MS 295 (M^+)

Ethyl 2-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-quinolin-3-carboxylate (X = 4-OCH_3)
from 1 g (4.17 mmol) ethyl 2-chloro-5,6,7,8-tetrahydro-quinoline-3-carboxylate and 1.28 g (8.34 mmol) (4-methoxybenzene)boronic acid;
yield: 520 mg (39 %); MS 311 (M^+)

General procedure for the preparation of imidazolines of the Examples 39 - 41 from the corresponding ethyl carboxylates



The ethyl carboxylate (1 eq.) was dissolved in 10 eq. of 1,2-diaminoethane and heated at 100 °C for 14 h. The excess of reactant was removed *in vacuo*, and remaining traces of the diamine were separated by running through a short column with silica gel (dichloromethane / ethanol 9:1). The resulting oil was dissolved in a mixture of hexamethyldisilazane (HMDS) and trimethylsilyl chloride (99:1), and it was heated to 100 °C for 80 h. After quenching with ethanol, the volatile components were removed *in vacuo* and the residue chromatographed on silica gel with dichloromethane / 10% ethanolic ammonia 95:5 to afford the title imidazoline.

The following compounds were synthesized according to this procedure:

Example 39: 2-(3-Chlorophenyl)-3-(4,5-dihydro-1H-imidazol-2-yl)- 5,6,7,8-tetrahydroquinoline (X = 3-Cl)

from 450 mg (1.43 mmol) of ethyl 2-(3-chlorophenyl)-5,6,7,8-tetrahydro-quinoline-3-carboxylate;

yield: 70 mg (15 %); beige resin; MS 311 (M^+)

Example 40: 3-(4,5-Dihydro-1H-imidazol-2-yl)-2-(4-methylphenyl)-5,6,7,8-tetrahydroquinoline (X = 4-CH_3)

from 520 mg (1.76 mmol) of ethyl 2-(4-methylphenyl)-5,6,7,8-tetrahydro-quinoline-3-carboxylate;

yield: 70 mg (13 %); beige resin; MS 291 (M^+)

Example 41: 3-(4,5-Dihydro-1H-imidazol-2-yl)-2-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline (X = 4-OCH_3)

from 520 mg (1.76 mmol) of ethyl 2-(4-methoxyphenyl)-5,6,7,8-tetrahydro-quinoline-3-carboxylate;

yield: 150 mg (30 %); beige resin; MS 307 (M^+)

The pharmacological activity of compounds of the present invention can be determined by methods well known in the art and by the assays disclosed herein.

ASSAYS

BTC6, F7 Insulinoma Cell Screening Models

BTC6,F7 are cultured in DMEM 4.5g/l glucose with the following supplements: 15%(v/v) equine serum; 2.5% (v/v) FCS; and 50 U/ml Penicillin/ 50 μg/ml Streptomycin.

A) Adherent BTC6,F7 cells

BTC6,F7 are seeded after trypsinization to 30.000 cells/well in a 96 well multiplate. The cells grow to 50 % confluence and at day 2 or 3 after seeding, the insulin secretion experiments were performed as follows:

Discard the supernatant of the 96 well plates after the cells have been seeded, wash 3 times with EBSS (Earl's balanced salt solution) (0 mM glucose)/ 0.1 % BSA and incubate in the EBSS solution 30 min at 5% CO_2, 37°C.

The experiments with the compounds were run in the presence of 10 mM glucose and also in the absence of glucose in different concentrations. Incubation time is 1 hour. The supernatante is filtered and the insulin amounts measured by radioimmunoassay using an antibody directed against rat insulin.

B) Dissociated BTC6,F7 cells

BTC6,F7 cells at 50 % confluence were dislodged using enzyme free cell dissociation solution. Dislodged cells were dissociated by pressing the cell suspension through a needle (25 gauge). Cells were washed three times in EBSS (0 mM glucose)/0.1% BSA and insulin secretion experiments are performed as described above.

Dose response titrations on the agonists described revealed EC_{50} values of < 10 mM, preferably < 1mmol.

Rat Islet Assay

The number of islets of three rats is usually sufficient to test 8 compounds including standards.

Solutions

1. 100 ml EBSS (Earl's balanced salt solution): For example, as commercially available Cat. No. BSS-008-B (Specialty Media) without Glucose & Phenol Red, with 0.1% BSA, other comparable commercially available media are acceptable.

2. 100 ml EBSS/BSA buffer + 130.8 mg D(+)-Glucose monohydrate (MW: 198.17)

(=3.3 mM final concentration).

3. 100 ml EBSS/BSA buffer + 661.8 mg D(+)-Glucose monohydrate (MW: 198.17)

(=16.7 mM final concentration).

4. 100 ml EBSS (Earl's balanced salt solution). For example, as commercially available,Cat. No. BSS-008-B (Specialty Media) without Glucose & Phenol Red, with 0.1% BSA, with 0.6 % DMSO; other comparable solutions may be used as well;

Dilution of compounds:

Each dilution of compound has to be double concentrated as it will be diluted 1 + 1 by EBSS/BSA + Glucose (either high Glucose, 16.7 mM final conc. or low Glucose, 3.3 mM final conc.) in a 24 -well tissue culture plate (or other appropriate tissue culture receptacle, if desired).

A stock solution of the compound to be tested of 10 mM in DMSO is made, and the following solutions made for the compounds to be tested, and for standards.

Tube No.	Concentration (μM)	final Concentration (μM)	Dilution (μl)
1	200	100	40 μl of stock + 2000 μl EBSS/BSA
2	60	30	900 μl of tube 1 + 2100 μl EBSS/BSA
3	20	10	300 μl of tube 1 + 2700 μl EBSS/BSA/ 0.6 % DMSO
4	6	3	300 μl of tube 2 + 2700 μl EBSS/BSA/

			0.6 % DMSO
5	2	1	300 µl of tube 3 + 2700 µl EBSS/BSA/ 0.6 % DMSO
6	0.6	0.3	300 µl of tube 4 + 2700 µl EBSS/BSA/ 0.6 % DMSO
7	0.2	0.1	300 µl of tube 5 + 2700 µl EBSS/BSA/ 0.6 % DMSO
8	0.06	0.03	300 µl of tube 6 + 2700 µl EBSS/BSA/ 0.6 % DMSO

Culture dishes are prepared (untreated, 100 x 20 mm, one per two compounds) with 10 ml EBSS/BSA and 10 ml low glucose EBSS/BSA or similar preparative solution and place in an incubator at 37°C, 5 % CO_2, for at least 15 min.

Preparation of Rat islets in culture dishes:

Approximately half of an islet is selected with a 100 µl pipette and transfered to a prepared culture dishe with EBSS/BSA/low Glucose by using binoculars (magnification about 30 x.

The dish is put back into the incubator (37°C, 5 % CO_2) for preincubation (30 min)

If a 24 well plate is used for the assay, the dilutions are distributed (500 µl each) as shown in the scheme below.

500 µl of EBSS/BSA + 0.6 % DMSO (0 = Control).

0 1	**0** 2	**0.03** 3	**0.03** 4	**0.1** 5	**0.1** 6
0.3 7	**0.3** 8	**1** 9	**1** 10	**3** 11	**3** 12
10 13	**10** 14	**30** 15	**30** 16	**0** 17	**0** 18
0.1 19	**0.1** 20	**1** 21	**1** 22	**10** 23	**10** 24

EBSS/BSA/ high Glucose, 500 μl is added to wells 1-16, and EBSS/BSA/ low Glucose, 500 μl is added to wells 17-24.

This scheme is repeated with the other compounds in tissue culture plates and the plates are placed into the incubator (37°C, 5 % CO_2) for at least 15 min.

The culture dish with the second half of the islets is taken out of the incubator. The rest of the islet is picked up with a 100 μl pipette and placed into the second of the prepared culture dishes with EBSS/BSA/low Glucose using binoculars, and placed back into the incubator (37°C, 5 % CO_2) for preincubation (30 min).

Take out the tissue culture plates 1 and 2 and the first preincubated islets. Place 8 islets into each well by using a 10 μl pipette and binoculars (general guideline-magnification about 40 x), generally trying to select islets of similar size which are not digested. The plates are placed back in the incubator (37°C, 5 % CO_2) for 90 min.

Remove the second of the overnight cultured culture dishes with islets from incubator. Approximately half of the islets are placed into the 3rd of the prepared culture dishes with EBSS/BSA/low Glucose with a 100 μl pipette and using binoculars (general guideline-magnification about 30 x), then placed back into the incubator (37°C, 5 % CO_2) for preincubation (30 min).

The 24 -well tissue culture plates 3 and 4 and the second preincubated islets culture dish are removed from the incubator and 8 islets placed into each well by using a 10 μl pipette and binoculars (magnification about 40 x), again selecting islets of similar size which are not digested. Put the plates back to the incubator (37°C, 5 % CO_2) for 90 min.

Take the culture dish with the second half of the islets out of the incubator. with a 100 μl pipette into the 4th of the prepared culture dishes with EBSS/BSA/low Glucose by using binoculars (magnification about 30 x) and put them back into the incubator (37°C, 5 % CO_2) for preincubation (30 min)

Take out the 24 -well tissue culture plates 5 and 6 and the 3rd preincubated islets culture dish. Place 8 islets into each well with a 10 μl pipette by using binoculars (magnification about 40 x). Put the plates back into the incubator (37°C, 5 % CO_2) for 90 min.

Take out the 24 -well tissue culture plates 7 and 8 and the last preincubated islets culture dish. Place 8 islets into each well with a 10 μl pipette by using binoculars (magnification about 40 x). Put the plates back to the incubator (37°C, 5 % CO_2) for 90 min.

When 90 minutes of incubation are over, transfer approximately 300 μl of each well into one well of the 96 well filter plate and by using a vacuum pump filter it into a 96 well Microplate. 4 of the 24 -well tissue culture plates cover one filterplate and

96-well-Microplate.

The insulin secreted by the islets is measured in a RIA after dilution (1:5).

Intravenous Glucose Tolerance Test

This test is used to examine in vivo efficacy of compounds of the present invention on insulin secretion and blood glucose at hyperglycemia.

The intravenous glucose tolerance test (IVGTT) is performed in overnight fasted anesthetized male wistar rats weighing 280-350g. Under pentobarbitone anesthesia (50 mg/kg ip) polyethylene catheters are placed in the left jugular vein and in the left common carotid artery. Glucose (10% solution) is administered intravenously at a dose of 0.5 g/kg, followed directly by an iv injection of the compound to be tested.

Blood samples are drawn before and 3, 6, 10, 15, 30 and 45 min after glucose administration, centrifuged and the obtained serum is stored at -20°C for analytics.

Test compounds are examined along with a reference (positive control) and a vehicle control with n=8 animals per group. Glucose is determined by the hexokinase method, and insulin via radioimmunoassay (RIA) from serum.

In order to examine the effects of test compounds on insulin and blood glucose at euglycemia in vivo, the protocol of the IVGTT as described above is used except for the administration of intravenous glucose.

The compounds of Formula I are preferably formulated prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of Formula I and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 to about 500 mg, more usually about .5 to about 200 mg, of the active ingredient. However, it will be understood that the therapeutic dosage administered will be determined by the physician in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, topical, intravenous, intramuscular or intranasal routes. For all indications, a typical daily dose will contain from about 0.05 mg/kg to about 20 mg/kg of the active compound of this invention. Preferred daily doses will be about 0.1 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg. However, for topical administration a typical dosage is about 1 to about 500 mg compound per cm^2 of an affected tissue. Preferably, the applied amount of compound will range from about 30 to about 300 mg/cm^2, more preferably, from about 50 to about 200 mg/cm^2, and, most preferably, from about 60 to about 100 mg/cm^2.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	25
starch, dried	425
magnesium stearate	10
Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 10 mg of active ingredient are made up as follows:

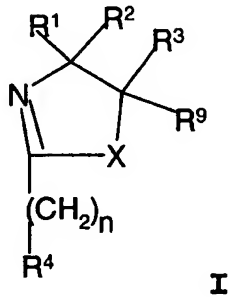
Active ingredient	10 mg
Starch	160 mg
Microcrystalline cellulose	100 mg
Polyvinylpyrrolidone (as 10% solution in water)	13 mg
Sodium carboxymethyl starch	14 mg
Magnesium stearate	3 mg
Total	300 mg

The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed through a sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since they are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention.

We claim

1. A compound of Formula (I) compounds of the following



I

wherein

R^1, R^2, R^3, and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together with the carbon atoms to which they are attached, combine to form a C_{3-7} carbocyclic ring and R^2 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together optionally form a bond and R^2 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^2, together with the carbon atom to which they are attached combine to form a C_{3-7} spirocarbocyclic ring and R^3 and R^9 are each independently hydrogen or C_{1-8} alkyl; or

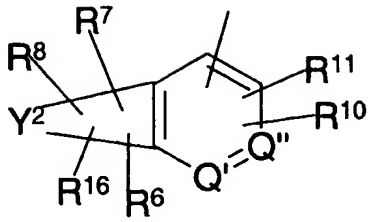
R^3 and R^9, together with the carbon atom to which they are attached, combine to form a C_{3-7} spirocarbocyclic ring and R^1 and R^2 are each independently hydrogen or C_{1-8} alkyl;

X is -O-, -S-, or $-NR^5-$;

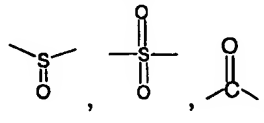
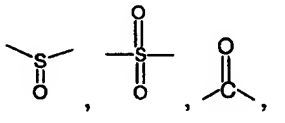
R^5 is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl, and an amino protecting group;

n is 0, 1, or 2;

R^4 is a group of the formula:



Q' and Q" are each independently selected from the group consisting of C, N, and N-O, provided that if one of Q' or Q" is N or N-O, then the other of Q' or Q" must be C, such that Q' and Q" cannot each simultaneously be selected from the group consisting of N and N-O;

Y^2 is $(CH_2)_{n'}$ wherein n' is 3, 4, 5, or 6; such that a 5- to 8- membered ring is formed to provide a bicyclic ring along with the benzene or pyrimidine group to which it is fused, which 5- to 8- membered ring is saturated, partially saturated or unsaturated and may optionally contain up to two atoms each independently selected from the group consisting of -O-, -S-,  , and $-NR^{12}-$, wherein each such optional -O-, -S-, atom or  , $-NR^{12}-$ groups replacing any one of the $-CH_2-$ groups comprising Y^2, provided that the resulting benzofused bicyclic ring is not an indole, and in which any of the $-CH_2-$ groups which comprise Y^2 may be substituted by R^6, R^7, R^8 or R^{16} provided that no more than four H atoms in Y^2 are replaced by said substitution and that the resulting benzofused bicyclic is not naphthalene or quinoline; and any two selected from the group consisting of R^6, R^7, R^8, R^{16} and R^{12} may optionally combine to form a bridge which is comprised of up to four carbon atoms provided that such bridge-forming two of R^6, R^7, R^8, R^{16} and R^{12}

are not bound to adjacent atoms, or together with the carbon atom to which they are attached may form a C_{3-7} spirocarbocyclic ring, in which one or two carbon atoms are optionally replaced by oxygen, sulfur, or NR^5, or together with the two adjacent carbon atoms to which they are attached R^6, R^7, R^8, R^{16} and R^{12} may form a C_{1-9} carbocyclic ring, in which one or two of the carbon atoms is optionally replaced by oxygen, sulfur or NR^5, and further provided that at least one of the group consisting of R^6, R^7, R^8, R^{16} and R^{12} is not hydrogen when X is NH, n is 0, and R^1, R^2, R^3, and R^9 are each hydrogen and Q' and Q'' are each C;

R^{12} is selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl, and an amino protecting group;

R^6 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, halo C_{1-8} alkylthio, C_{1-8} alkylsulfinyl, C_{1-8} alkylsulfonyl, C_{3-7} cycloalkoxy, aryl-C_{1-8} alkoxy, halo, halo-C_{1-8} alkyl, halo- C_{1-8} alkoxy, nitro, $-NR^{14}R^{15}$, $-CONR^{14}R^{15}$, aryl C_{1-8} alkyl, optionally substituted heterocyclyl, optionally substituted phenyl, optionally substituted naphthyl, C_{1-8} acylamino, haloC_{1-8} acylamino, cyano, hydroxy, COR^{13}, $COOR^{13}$, halo C_{1-8} alkylsulfinyl, halo C_{1-8} alkylsulfonyl, and alkoxyalkyloxy of the formula $CH_3(CH_2)_p$-O-$(CH_2)_q$-O-;

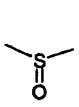
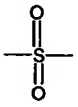
R^7, R^8, and R^{16} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, halo, halo-C_{1-8} alkyl, halo-C_{1-8} alkoxy, optionally substituted phenyl, optionally substituted naphthyl, and optionally substituted heteroaryl;

R^{10} is selected from the group consisting of hydrogen, halo, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cycloalkyl-C_{1-8} alkoxy, halo-C_{1-8} alkyl,

halo-C_{1-8} alkoxy, C_{1-8} alkoxy, carbo-C_{1-8} alkoxy, optionally substituted aryl, and optionally substituted heteroaryl;

R^{11} is selected from the group consisting of hydrogen, halo, C_{1-8} alkoxy, C_{3-7}-cycloalkyl, C_{3-7} cycloalkyl-C_{1-8} alkoxy, C_{1-8} alkyl, C_{3-7} cycloalkoxy, hydroxy, halo C_{1-8} alkoxy, carbo-C_{1-8} alkoxy, optionally substituted phenyl, optionally substituted phenyl-C_{1-8} alkyl, optionally substituted phenyloxy, optionally substituted phenyl-C_{1-8} alkoxy, (tetrahydropyran-2-yl)methoxy, C_{1-8} alkyl-$S(O)_m$, optionally substituted aryl-C_{1-8} alkyl-$S(O)_{m'}$, $CH_3(CH_2)_{p'}$-Z^1-$(CH_2)_{q'}$-Z^2-, and Z^3-$(CH_2)q''$-Z^2-;

where

Z^1 and Z^2 are each independently a bond, -O-, -S-,  ,  , sulphoximino, or $NR^{14'}$,

Z^3 is hydroxy, protected hydroxy, $NR^{14'}R^{15'}$, protected amino, SH, or protected SH;

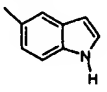
R^{13} is hydrogen, C_{1-8} alkyl, or optionally substituted phenyl;

R^{14} , $R^{14'}$ R^{15} and $R^{15'}$ are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl C_{1-8} alkyl, optionally substituted phenyl, or R^{14} and R^{15} or $R^{14'}$ and $R^{15'}$, respectively, together with the nitrogen atom to which they are attached may combine to form a heterocyclic ring comprising the nitrogen and C_{2-6} alkyl, wherein C_{2-6}alkyl is optionally substituted with one or two C_{1-8} alkyl groups or one carbon atom of the heterocyclic ring is optionally replaced by -O- or -S-;

p and p' are each independently selected from the group consisting of 0, 1, 2, 3, and 4;

q, q', and q''' are each independently selected from the group consisting of 1, 2, 3, 4, and 5;

m, m', and m'' are each independently selected from the group consisting of 0, 1 and 2;

provided that when R^1, R^2, R^3, and R^9 are each hydrogen, X is NH, n is 0, then R^4 is not 4-(benzothiazol-2-yl)benzyl or a group of the formula:  ;

and pharmaceutically acceptable salts and esters thereof.

2. A compound according to Claim 1 wherein R^1 and R^2 are each hydrogen and R^3 and R^9 are each hydrogen or methyl.

3. A compound according to Claim 2 wherein X is -NH-.

4. A compound according to Claim 2 wherein X is S and n is 1.

5. A compound according to either of Claims 2 and 3 wherein n is 0.

6. A compound according to Claim 5 wherein R^{11} is $H_3C(CH)_{p'}$-O-$(CH)_{q'}$-O-.

7. A compound according to any one of the preceding claims wherein Q^1 and Q^2 are each C.

8. A compound according to either of Claims 2 or 5 in which R^4 is a coumarin group or a quinolone group.

9. A pharmaceutical formulation comprising a compound according to any of Claims 1 to 8 or a pharmaceutically acceptable salt or ester thereof, together with a pharmaceutically acceptable carrier or diluent therefor.

10. A compound according to Claim 1 or a pharmaceutically acceptable salt or ester thereof, for use as a pharmaceutical.

11. A compound according to Claim 1 or a pharmaceutically acceptable salt or ester thereof, for use in the manufacture of a medicament for the treatment of a mammal for diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present.